

Dysfunction of the canine respiratory muscle pump in ascites

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Leduc D, De Troyer A. Dysfunction of the canine respiratory muscle pump in ascites. *J Appl Physiol* 102: 650–657, 2007. First published November 9, 2006; doi:10.1152/jappphysiol.00798.2006.—Ascites, a complicating feature of many diseases of the liver and peritoneum, commonly causes dyspnea. The mechanism of this symptom, however, is uncertain. In the present study, progressively increasing ascites was induced in anesthetized dogs, and the hypothesis was initially tested that ascites increases the impedance on the diaphragm and, so, adversely affects the lung-expanding action of the muscle. Ascites produced a gradual increase in abdominal elastance and an expansion of the lower rib cage. Concomitantly, the caudal displacement of the diaphragm and the fall in airway opening pressure during isolated stimulation of the phrenic nerves decreased markedly; transdiaphragmatic pressure during phrenic stimulation also decreased. To assess the adaptation to ascites of the respiratory system overall, we subsequently measured the changes in lung volume, the arterial blood gases, and the electromyogram of the parasternal intercostal muscles during spontaneous breathing. Tidal volume and minute ventilation decreased progressively as ascites increased, leading to an increase in arterial PCO₂ and parasternal intercostal inspiratory activity. It is concluded that 1) ascites, acting through an increase in abdominal elastance and an expansion of the lower rib cage, impairs the lung-expanding action of the diaphragm; 2) this impairment elicits a compensatory increase in neural drive to the inspiratory muscles, but the compensation is not sufficient to maintain ventilation; and 3) dyspnea in this setting results in part from the dissociation between increased neural drive and decreased ventilation.

respiratory muscles; diaphragm; intercostal muscles

ASCITES IS A COMMON COMPLICATING feature of many diseases of the liver and peritoneum, and its occurrence is frequently associated with dyspnea (1, 4, 31). Inasmuch as the symptom is relieved after the amount of liquid in the abdominal cavity is reduced by paracentesis, one can safely conclude that it is primarily related to abdominal distension per se, rather than the underlying disease. However, even though ascites is well known to cause a reduction in lung volume (1, 3, 5), the mechanism of dyspnea in this setting is uncertain.

Several attempts have been made to assess the effects of ascites on the function of the inspiratory muscle pump in humans and to evaluate the potential role of a pump dysfunction in causing dyspnea, but these studies have provided conflicting results. Specifically, Prezant et al. (29) reported an increase in pressure during maximum static inspiratory efforts in six patients with chronic renal failure receiving 3 liters of peritoneal dialysate. On the other hand, Siafakas et al. (32) reported that 2 liters of dialysate in similar patients caused a small reduction in pressure, and Duranti et al. (16) found no change in pressure after removal of 3.5–13.0 liters of ascites in

eight patients with cirrhosis. However, in most patients, the amount of liquid in the peritoneal cavity was small and unlikely to impact significantly on the respiratory system. In addition, because the pressure measurements in these studies were obtained during voluntary efforts, they had a strong volitional component that could be affected by the nature and severity of the underlying disease process.

This volitional component was eliminated in the study by Hubmayr et al. (20). In their attempt to identify the determinants of the pressure-generating ability of the diaphragm, these investigators measured transdiaphragmatic pressure (P_{di}) during isolated stimulation of the phrenic nerves in anesthetized dogs, first before and then after introduction of Ringer solution (60–100 ml/kg body wt) into the abdominal cavity. They found that the liquid introduction elicited an expansion of the lower rib cage, together with a cranial displacement and a small lengthening of the relaxed diaphragm. P_{di} during phrenic nerve stimulation was also slightly increased. However, the volume of ascites in this study was equivalent to 4–7 liters in a 70-kg human subject. Therefore, although this volume was greater than that in patients on peritoneal dialysis (29, 32), it was still moderate compared with that in patients with cirrhosis or peritoneal metastases. More importantly, Hubmayr et al. did not report on the separate pressure changes on the pleural and abdominal side of the diaphragm. Consequently, as for the human studies previously discussed (16, 29, 32), it is difficult to relate the findings of this study to dyspnea.

The present study was initially undertaken to test the hypothesis that severe ascites increases the impedance on the diaphragm and, thereby, impairs the lung-expanding action of the muscle. Thus progressively increasing ascites was induced in dogs, and the changes in pleural pressure and abdominal pressure (P_{ab}), as well as the displacements of the diaphragm, were examined during isolated stimulation of the phrenic nerves in the neck. The results confirmed that severe ascites has a marked detrimental effect on the lung-expanding action of the diaphragm, and this prompted us subsequently to evaluate how the respiratory muscle pump overall adapts to this impairment and performs the act of breathing.

METHODS

The experiments, which were approved by the Animal Ethics and Welfare Committee of the Brussels School of Medicine, were carried out on 14 pentobarbital sodium-anesthetized (initial dose 30 mg/kg iv) adult cross-breed dogs (19–31 kg body wt). The animals were placed in the supine posture, intubated with a cuffed endotracheal tube, and connected to a mechanical ventilator (Harvard Pump, Chicago, IL). A venous cannula inserted into the forelimb was used to administer

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maintenance doses of anesthetic and a catheter inserted into a femoral artery was used to monitor blood pressure and sample arterial blood periodically for blood gas analysis. The abdomen was then opened by a midline incision from the xiphisternum to the umbilicus, and a balloon-catheter system filled with 1.0 ml of air was placed between the liver and the stomach for measurement of Pab. In each animal, a catheter was also inserted through the right external oblique and internal oblique muscles of the abdomen, midway between the costal margin and the iliac crest, such that liquid could easily be introduced into the abdominal cavity later, and in four animals, rows of five lead spheres (4–5 mm diameter) were stitched to the peritoneal surface and superficial muscle fibers of the left and right hemidiaphragms in the coronal midplane to assess the changes in diaphragm silhouette and muscle length. This technique has been previously described in detail (13, 14). Thus, typically, the markers attached to the cranial half of the muscle were spaced at ~15- to 20-mm intervals, and those attached to the caudal half, in the zone of apposition of the diaphragm to the rib cage (27), were spaced at ~25- to 30-mm intervals. Consequently, the chord length between the successive markers closely approximated the arc length along the diaphragm. The abdomen was finally sutured in two layers, and two experimental protocols were followed.

Experiment 1. Six animals were studied first to evaluate the effects of ascites on the elastance of the abdomen, the pressure-generating ability of the diaphragm, and the silhouette and length of the muscle during isolated contraction. In each animal, the C₅ and C₆ phrenic nerve roots were isolated bilaterally in the neck 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 the change in airway opening pressure (ΔP_{ao}). A long inextensible thread was also attached to the abdominal suture and led ventrally, perpendicular to the coronal plane, over a pulley placed above the animal, and it was connected to a linear displacement transducer (Schaevitz Engineering, Pennsauken, NJ) to measure the changes in the anteroposterior (AP) diameter of the abdomen.

The animal was allowed to recover for 15 min after instrumentation, after which it was made apneic by mechanical hyperventilation. Abdominal elastance was then assessed by measuring the changes in Pab and AP diameter of the abdomen during passive inflation of the respiratory system. Five levels of inflation (200, 400, 600, 800, and 1,000 ml) were applied in duplicate. When this procedure was completed, the animal was reconnected to the ventilator and hyperventilated. After the ventilator was stopped, the endotracheal tube was occluded at resting end expiration [functional residual capacity (FRC)], and the changes in Pao and Pab generated by bilateral, tetanic stimulation of the C₅ and C₆ phrenic nerve roots were measured; the stimuli were square pulses of supramaximal voltage, 0.1-ms duration and 20-Hz frequency. Two trials of stimulation were performed. AP radiographs of the lower rib cage and upper abdomen were also taken in the four animals with markers along the diaphragm, first during relaxation at FRC and then during stimulation of the phrenic nerves.

After completion of these measurements, a volume of liquid corresponding to 25 ml/kg body wt was introduced into the abdominal cavity, and measurements of abdominal elastance and pressure changes produced by phrenic nerve stimulation were repeated. Liquid volume was subsequently increased by increments of 25 ml/kg body wt to a total of 200 ml/kg, and measurements of abdominal elastance and pressure changes during phrenic nerve stimulation were obtained after each infusion. Chest radiographs during relaxation and during phrenic nerve stimulation were also taken at 50, 100, 150, and 200 ml/kg. The liquid introduced into the abdominal cavity (Dianal glucose 1.36%, Baxter) was isosmotic, so its volume after injection remained stable.

In each animal, liquid was finally removed from the abdominal cavity, such that the total volume of ascites was brought back to 100 ml/kg, and the changes in Pao and Pab during phrenic nerve stimulation were measured again. The pressure changes in this condition

were only $8.2 \pm 3.7\%$ (range -10.0 to $+10.0\%$) different from those obtained during the initial measurement, thus indicating that the phrenic nerve preparation was stable.

Experiment 2. Eight animals were next studied to assess the response of the respiratory muscle pump to the diaphragmatic dysfunction induced by ascites (see RESULTS). The phrenic nerve roots in these animals were left intact, but the vagi were isolated in the neck and sectioned to avoid the tachypnea that ascites, acting through the decrease in FRC and the increase in vagal afferent inputs from the lung, would probably elicit otherwise. Also, the rib cage and intercostal muscles were exposed on the right side of the chest from the second to the ninth rib by deflection of the skin and underlying muscle layers, and a pair of silver hook electrodes spaced 3–4 mm apart was inserted into the third interspace to record the electromyogram (EMG) of the parasternal intercostal muscle. The electrodes were inserted in parallel fibers in the muscle bundles situated near the sternum, i.e., in the muscle area with the greatest inspiratory drive (15, 23). The EMG signal was processed with an amplifier (model 830/1, CWE, Ardmore, PA), band-pass filtered below 100 and above 2,000 Hz, and rectified before its passage through a leaky integrator with a time constant of 0.2 s. In each animal, a hook was also screwed into the fourth rib in the midaxillary line and connected to a linear displacement transducer (Schaevitz Engineering) to measure the craniocaudal (axial) displacement of the ribs during breathing, and a heated Fleisch pneumotachograph coupled with a differential pressure transducer was connected to the endotracheal tube to measure the changes in lung volume.

After 30 min of recovery, baseline measurements of tidal volume, Pab, rib motion, and parasternal EMG activity during resting breathing were obtained. After two runs of 15 breaths were recorded over a 20-min period, liquid was introduced into the abdominal cavity. Liquid volume was increased by increments of 50 ml/kg to a total of 200 ml/kg. As during control, two runs of resting breathing were obtained in each condition. Earlier studies clearly established that prolonged anesthesia in dogs causes the gradual development of atelectasis and a decrease in pulmonary compliance (9, 27). To eliminate the confounding influence of this factor on the response to ascites, the animal in each condition was given a series of 10 large passive inflations before the measurements were obtained.

The animals in *experiment 1* were maintained at a constant, rather deep, level of anesthesia throughout the observation. They had no corneal reflex, no movements of the fore- or hindlimbs, and no changes in heart rate and blood pressure, including during phrenic nerve stimulation. In contrast, to avoid obscuring the response studied, in *experiment 2*, we regulated anesthesia such that the animals' blink and corneal reflexes were present throughout the measurements. Rectal temperature in these animals was also maintained constant between 36 and 38°C with infrared lamps. At the end of the experiment, the animal was given an overdose of anesthetic (30–40 mg/kg iv).

Data analysis. For each volume of ascites in each animal of *experiment 1*, the increases in Pab and AP diameter of the abdomen during passive inflation were averaged over the two trials, and the slope of the relation between the two variables was calculated by linear regression techniques (coefficient of correlation = 0.952–0.999) to yield abdominal elastance. The pressure changes obtained during phrenic nerve stimulation were also averaged over the two trials, and the displacements of the diaphragm were assessed in two ways, as previously described (13, 14). 1) The contours of the muscle were traced during relaxation and during stimulation; all contours were related to a metallic marker that was attached to the sling on the side of the animal and was, therefore, stationary. For each volume of ascites, the contour during phrenic nerve stimulation was then superimposed on that during relaxation, and the axial displacement of the diaphragmatic dome in the two sagittal planes situated midway between the spinous processes of the vertebrae and the lateral rib cage margins was measured. The perpendicular distance from the sagittal midplane to the lateral margin of the lower rib cage during stimulation

was also measured to provide an estimate of the radius of the ring of insertion of the diaphragm into the lower rib cage. 2) Diaphragmatic muscle length in each condition was 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, however, the changes in muscle length during stimulation were expressed as percent changes relative to the muscle length during relaxation (L_r). Because phrenic nerve stimulation produced identical length changes in the right and left hemidiaphragms and identical displacements of the domes, these changes were averaged for each individual animal.

For each volume of ascites in each animal of *experiment 2*, tidal volume, ΔP_{ab} , the inspiratory axial displacement of the rib, and phasic inspiratory EMG activity in the parasternal intercostal muscle were averaged over 10 consecutive breaths from each run. Inspiratory EMG activity was first quantified by measuring the peak height of the integrated EMG signal in arbitrary units, and it was then expressed as a percentage of the activity recorded before ascites (control). In addition, inspiratory time (T_i) was measured from the onset of the parasternal intercostal EMG until peak activity, and the peak deflection of the integrated EMG signal was also divided by T_i to obtain the average rate of rise of inspiratory activity.

Data were finally averaged across the animal group, and they are presented as means \pm SE. ANOVA with repeated measures was used for statistical analysis of the effects of increasing ascites on abdominal elastance, pressure, diaphragm displacement, and diaphragm muscle length (*experiment 1*), and Student-Newman-Keuls tests were used, when appropriate, for multiple comparison testing of the mean values. Statistical assessment of the effects of ascites on tidal volume, ΔP_{ab} , axial rib displacement, and parasternal intercostal EMG activity during spontaneous breathing (*experiment 2*) was made similarly. The criterion for statistical significance was taken as $P < 0.05$.

RESULTS

Abdominal elastance. The effects of increasing ascites on the relation between AP diameter of the abdomen and Pab during passive inflation are illustrated by the data from a representative animal in Fig. 1A, and the values of abdominal elastance measured for all volumes of ascites in the six animals are shown in Fig. 1B. The relation between AP diameter of the abdomen and Pab remained essentially unchanged until ascites was 50 ml/kg. However, as the volume of ascites was increased further, the relation was altered, such that, for a given rise in Pab, the increase in diameter was smaller. As a result, whereas abdominal elastance in the control condition averaged 0.44 ± 0.07 cmH₂O/mm, with increasing ascites it increased progressively and continuously, such that at 200 ml/kg, it was 7.39 ± 1.43 cmH₂O/mm ($P < 0.001$).

Pressure-generating ability of the diaphragm. ΔP_{ao} and ΔP_{ab} during phrenic nerve stimulation in the different conditions are shown in Fig. 2. ΔP_{ao} remained unchanged until ascites was 50 ml/kg, and it then decreased progressively and continuously as ascites was increased from 75 to 200 ml/kg ($P < 0.001$). At 200 ml/kg, therefore, ΔP_{ao} was only $25.5 \pm 3.3\%$ of the control value. In contrast, ΔP_{ab} increased with increasing ascites up to 125 ml/kg ($P < 0.001$) and then decreased as ascites was increased further. As a result, ΔP_{di} ($\Delta P_{ab} - \Delta P_{ao}$) remained unchanged until ascites was 100 ml/kg and decreased progressively from 59.8 ± 5.0 to 33.3 ± 4.7 cmH₂O as ascites was increased from 100 to 200 ml/kg ($P < 0.001$).

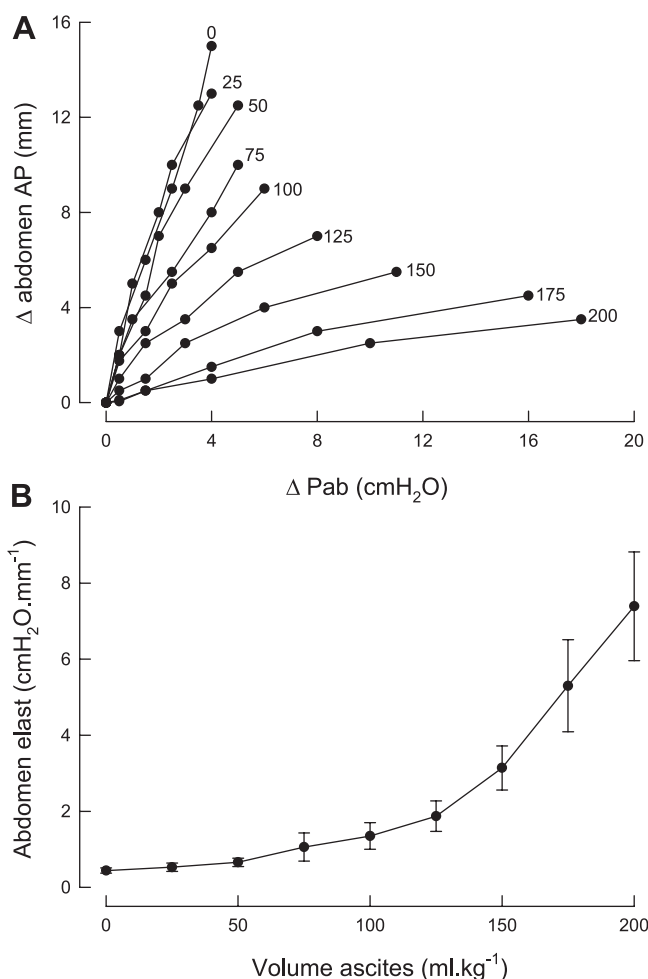


Fig. 1. A: increase in anteroposterior (AP) diameter of the abdomen vs. rise in abdominal pressure (Pab) during passive inflation (200–1,000 ml) in the presence of ascites (0–200 ml/kg body wt) in a representative animal. B: progressive increase in abdominal elastance as ascites increased from 50 to 200 ml/kg body wt. Values are means \pm SE from 6 animals.

Displacement and length of the diaphragm during isolated stimulation. With increasing ascites, the dome of the diaphragm at rest was progressively displaced in the cranial direction, such that muscle length increased. This increase, however, was small and averaged, for the four animals, $3.4 \pm 2.5\%$ of the control FRC length. However, even though phrenic nerve stimulation caused a large muscle shortening and a large caudal displacement of the dome in all conditions, the amount of muscle shortening decreased markedly and continuously ($P < 0.001$) with increasing ascites (Fig. 3). Thus, whereas muscle shortening in the control condition was $32.7 \pm 3.1\% L_r$, with ascites of 200 ml/kg, it was only $11.5 \pm 2.1\% L_r$. The caudal displacement of the dome also decreased progressively from 43.6 ± 1.5 mm in the control condition to 10.3 ± 1.0 mm at 200 ml/kg ($P < 0.001$). Concomitantly, the radius of the ring of insertion of the diaphragm into the lower rib cage increased gradually ($P < 0.001$; Fig. 4).

Spontaneous breathing. The effects of ascites on the pattern of breathing are illustrated by records from a representative animal in Fig. 5, and tidal volume, breathing frequency, and arterial blood gases for the different volumes of ascites in the eight animals are shown in Fig. 6. No alteration in tidal volume

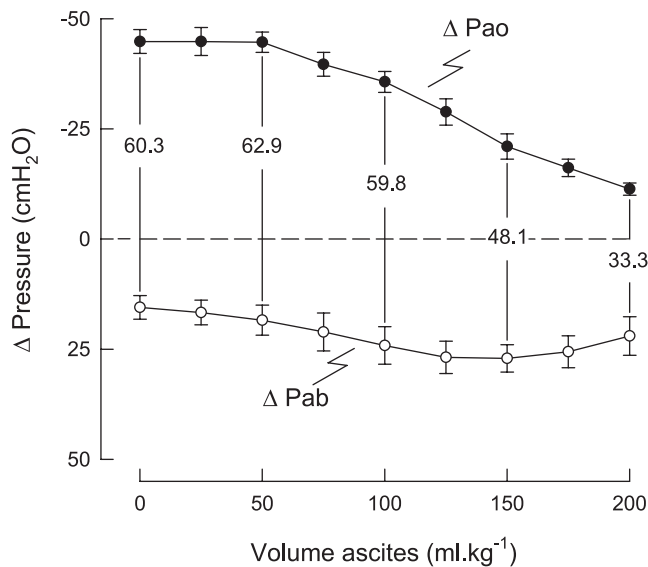


Fig. 2. Changes in airway opening pressure (ΔP_{ao}) and Pab (ΔP_{ab}) during bilateral tetanic (20-Hz) stimulation of C_5 and C_6 phrenic nerve roots in the presence of ascites. Vertical distance between ΔP_{ao} and ΔP_{ab} at any given volume of ascites corresponds to change in transdiaphragmatic pressure ($\Delta P_{di} = \Delta P_{ab} - \Delta P_{ao}$); values along vertical bars at 0, 50, 100, 150, and 200 ml/kg thus correspond to ΔP_{di} . Note marked, continuous decrease in ΔP_{ao} with increasing ascites and progressive increase in ΔP_{ab} as ascites was increased from 0 to 125 ml/kg body wt. As ascites was increased further, however, ΔP_{ab} also decreased. As a result, ΔP_{di} decreased as well. Values are means \pm SE from 6 animals.

or breathing frequency occurred when ascites was 50 ml/kg. However, as ascites was increased further, tidal volume decreased progressively and markedly in every animal ($P < 0.001$). Thus, whereas tidal volume in the control condition

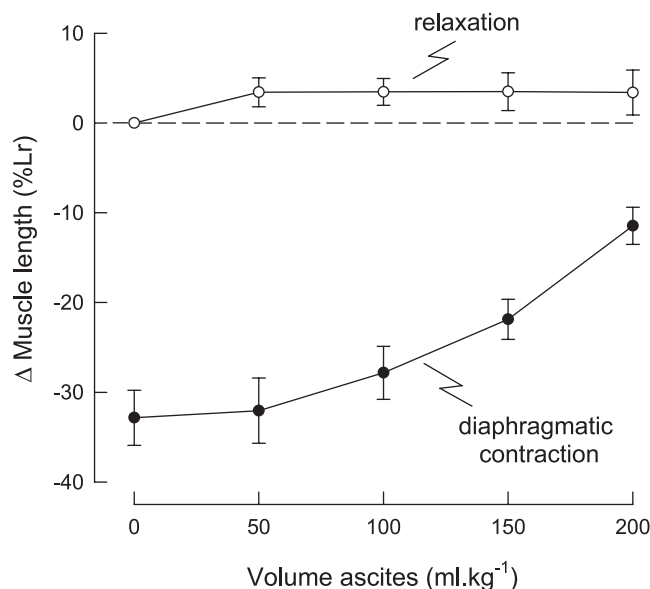


Fig. 3. Changes in diaphragm muscle length during relaxation and tetanic (20-Hz) stimulation of C_5 and C_6 phrenic nerve roots in the presence of ascites. Changes in muscle length during stimulation are expressed as percent changes relative to muscle length during relaxation (L_r). Negative changes in muscle length indicate muscle shortening. Note small increase in muscle length during relaxation with increasing ascites and marked decrease in muscle shortening during phrenic stimulation. Values are means \pm SE from 4 animals.

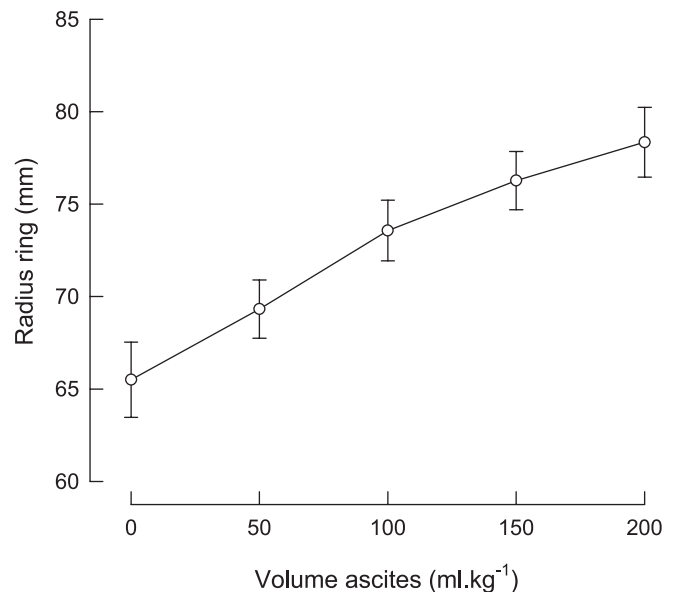


Fig. 4. Radius of the lower part of the rib cage during bilateral stimulation of C_5 and C_6 phrenic nerve roots. Note progressive increase in radius with increasing ascites. Values are means \pm SE from 4 animals.

was 455 ± 41 ml, with an ascites of 200 ml/kg it was only 235 ± 15 ml (Fig. 6A). Concomitantly, breathing frequency increased from 8.9 ± 1.5 to 9.9 ± 1.3 breaths/min (Fig. 6B), but this increase did not reach the level of statistical significance. As a result, minute ventilation also decreased from 3.75 ± 0.4 l/min in the control condition to 2.30 ± 0.26 l/min at 200 ml/kg ($P < 0.001$), and arterial P_{CO_2} increased gradually ($P < 0.001$) from 41.1 ± 2.9 to 55.2 ± 2.9 Torr (Fig. 6C). Arterial P_{O_2} , however, remained similar to the control value (91.5 ± 4.5 Torr) or increased slightly above the control value until ascites was 150 ml/kg (Fig. 6D); at 200 ml/kg, a small decrease in arterial P_{O_2} to 83.2 ± 8.7 Torr ($P < 0.02$) was observed.

Figure 5 also shows the effects of ascites on the EMG activity of the parasternal intercostal muscle. With increasing ascites, parasternal inspiratory activity gradually increased in all animals ($P < 0.001$), such that at 200 ml/kg, the peak height of the integrated EMG signal amounted to $145.7 \pm 12.2\%$ of the control value (Fig. 7A). Because T_i was essentially unaltered, the rate of rise of parasternal intercostal activity also increased progressively to $140.1 \pm 9.9\%$ at 200 ml/kg ($P < 0.001$). Similarly, the inspiratory cranial displacement of the ribs increased gradually ($P < 0.001$) from 3.68 ± 0.41 mm in the control condition to 7.51 ± 0.59 mm at 200 ml/kg (Fig. 7B), and ΔP_{ab} increased ($P < 0.001$) from 2.86 ± 0.30 cmH₂O during control to 4.86 ± 0.80 cmH₂O at 150 ml/kg (Fig. 7C). As ascites was increased to 200 ml/kg, however, ΔP_{ab} decreased slightly to 4.46 ± 0.79 cmH₂O.

DISCUSSION

Because ascites causes a cranial displacement and an increase in length of the relaxed diaphragm (20, 29), it should cause an increase in passive diaphragmatic tension. Moreover, to the extent that ascites distends the peritoneal cavity, it should also stretch the muscles of the ventrolateral wall of the abdomen and elicit passive tension in these muscles. As a

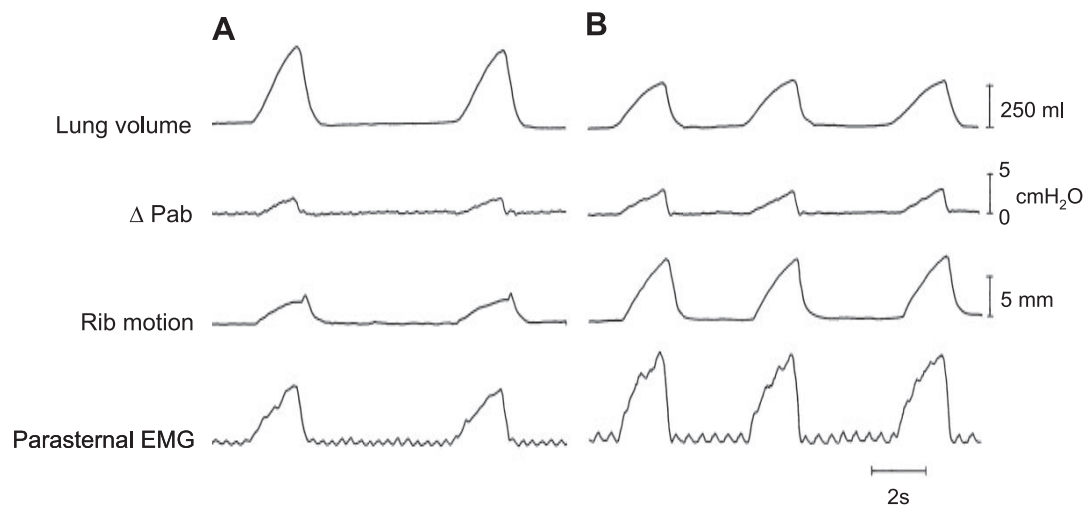


Fig. 5. Traces of lung volume, ΔP_{ab} , axial displacement of the 4th rib (rib motion; cranial displacement upward), and parasternal intercostal EMG activity (integrated signal) obtained from a representative animal during resting, room air breathing in the control condition (A) and in the presence of ascites (200 ml/kg; B). Note marked decrease in tidal volume, increase in parasternal intercostal inspiratory activity, and increase in inspiratory cranial displacement of the rib with ascites.

result, in agreement with the observation by Mutoh et al. (28) that chest wall compliance in pigs decreases during inflation of a balloon placed in the abdominal cavity, it was expected that ascites would lead to an increase in the elastance of the abdominal compartment of the chest wall. In addition, a recent

study of the interaction between the diaphragm and intercostal muscles has led to the development of a simple, two-compartment model of the chest wall (12), and according to this model, ΔP_{ao} during isolated contraction of the diaphragm would be related to the effective pressure (or force) exerted by the

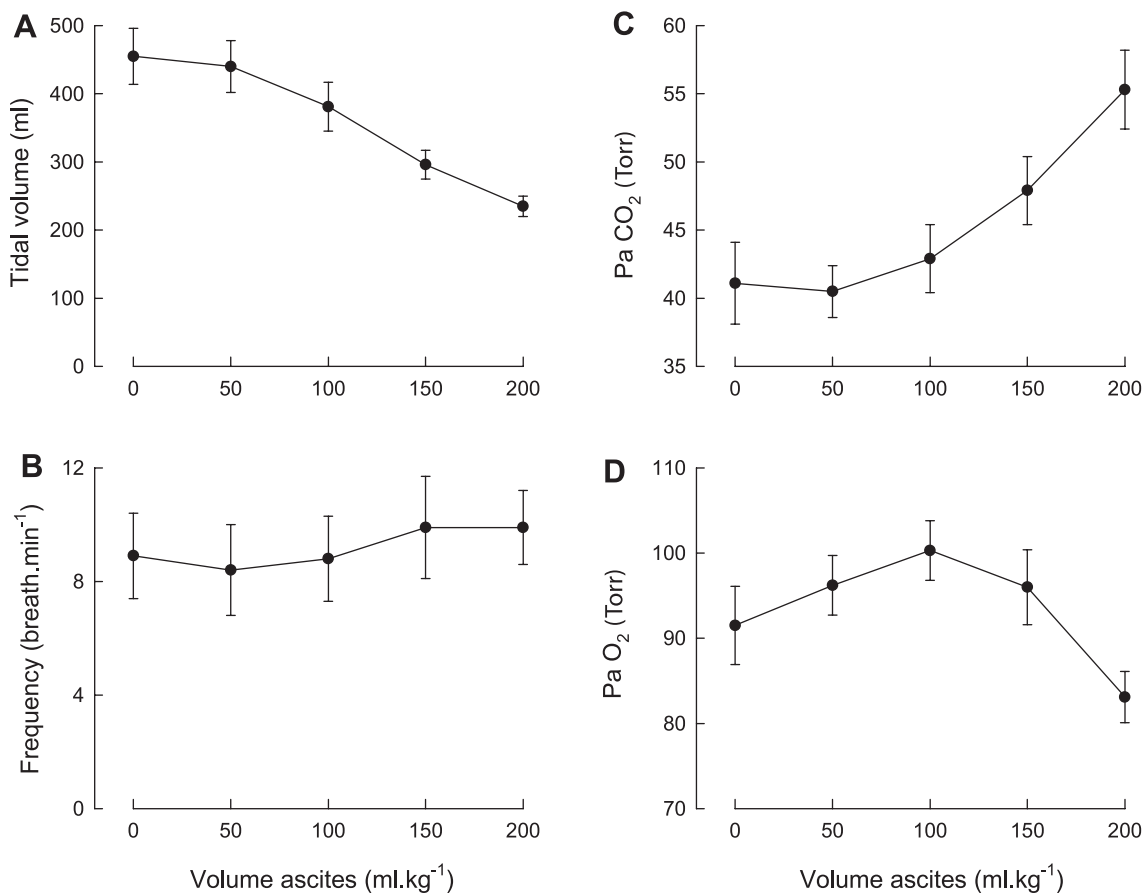


Fig. 6. Tidal volume (A), breathing frequency (B), arterial PCO₂ (PaCO₂, C), and arterial PO₂ (PaO₂, D) during resting breathing in the presence of ascites. Note marked, progressive decrease in tidal volume and increase in PaCO₂ as ascites was increased from 50 to 200 ml/kg. Values are means \pm SE from 8 animals.

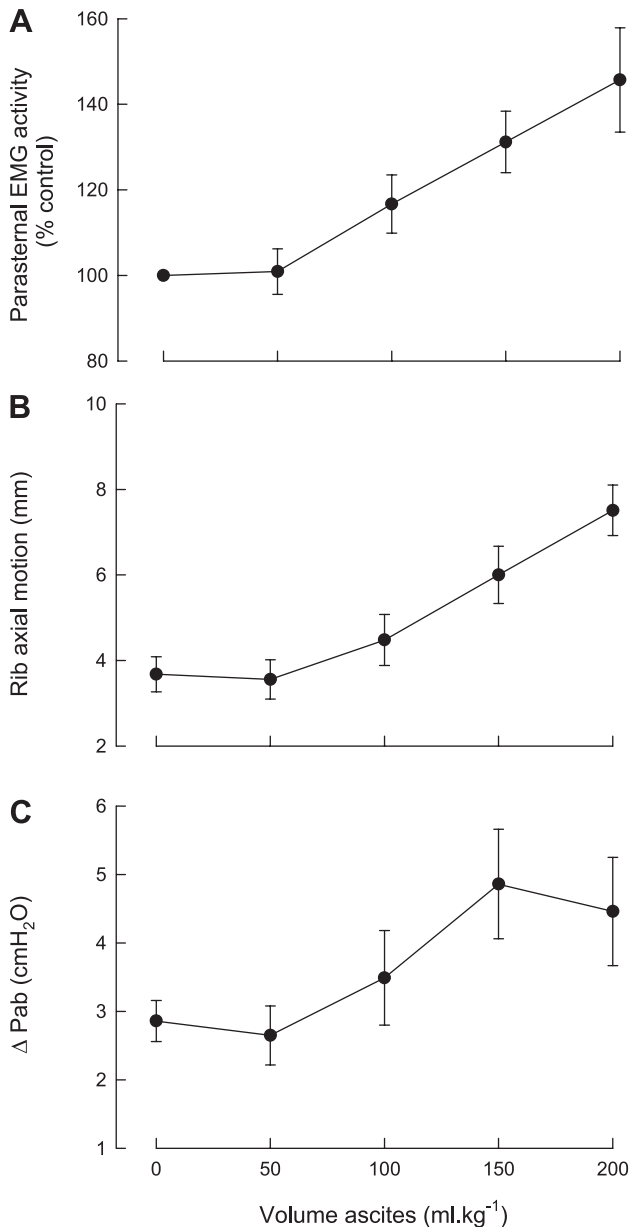


Fig. 7. Parasternal intercostal inspiratory activity (A), inspiratory cranial rib displacement (B), and ΔP_{ab} (C) during resting breathing in the presence of ascites. Parasternal intercostal activity is expressed as percentage of activity recorded in the control condition. Note gradual increase in parasternal intercostal activity with increasing ascites and progressive increase in inspiratory cranial displacement of the ribs and ΔP_{ab} . As ascites increased from 150 to 200 ml/kg body wt, ΔP_{ab} decreased slightly. Values are means \pm SE from 8 animals.

muscle (P_A) and to the elastance of the rib cage (K_R) and abdominal (K_A) compartments, such that

$$\Delta P_{ao} = -[K_R/(K_R + K_A)]P_A \quad (1)$$

If ascites did cause an increase in K_A , one would therefore predict that, during isolated diaphragm contraction, ΔP_{ao} would be smaller for a given P_A .

In agreement with our hypothesis, every animal of the study showed a progressive increase in abdominal elastance as the volume of ascites was increased (Fig. 1). Every animal also

showed a gradual decrease in ΔP_{ao} during isolated phrenic nerve stimulation (Fig. 2), thus confirming that ascites does adversely affect the lung-expanding action of the diaphragm. The values of ΔP_{di} obtained in these animals suggest, however, that a factor other than the increase in abdominal elastance operates to impair diaphragmatic function in this condition. Thus the relaxed diaphragm in supine dogs is near its optimum force-producing length (17, 30), and, with ascites, its muscle fibers lengthened 3–4% (Fig. 3). To the extent that the muscle fibers still shortened by 11% during phrenic nerve stimulation with severe ascites, the conclusion can therefore be drawn that these fibers continued to operate on the ascending portion of their length-tension characteristics (17, 25, 30). Furthermore, the finding that the amount of diaphragm shortening during stimulation decreased with ascites (Fig. 3) implies that the diaphragmatic fibers during contraction were longer. Consequently, the tension developed by the muscle in response to a given activation should be greater; hence, one would expect that ΔP_{di} would be greater and that the adverse effect of abdominal elastance on ΔP_{ao} would be partly offset. In fact, although the increase in abdominal elastance with moderate ascites induced an increase in ΔP_{ab} during phrenic nerve stimulation, this increase was relatively small and hardly compensated for the loss in ΔP_{ao} . As a result, ΔP_{di} remained essentially unchanged. When ascites was severe, ΔP_{ab} even decreased, such that ΔP_{di} decreased as well.

Boriek et al. (6) examined the determinants of P_{di} in dogs. Measuring the changes in diaphragm length and diaphragm curvature as well as ΔP_{di} , these investigators showed that curvature remained virtually constant during spontaneous inspiratory efforts at different lung volumes. They concluded, therefore, that ΔP_{di} during such efforts was exclusively related to muscle length. However, they also predicted that an expansion of the lower rib cage would induce a decrease in diaphragm curvature and, with it, a decrease in the pressure developed. Such a lower rib cage expansion has previously been shown to occur with ascites (20), and it was also seen in the present study. Thus, when the volume of ascites in our animals was set at 200 ml/kg, the radius of the ring of insertion of the diaphragm to the lower rib cage was 23% greater than during control (Fig. 4), and the analysis of Boriek et al. would predict that, for a given muscle tension, such an increase would lead to a 25% reduction in ΔP_{di} . Although the decrease in ΔP_{di} for this volume of ascites exceeded the predicted value by a factor of ~ 2 , this result supports the idea that, in severe ascites, the loss in the lung-expanding action of the diaphragm is, in part, the result of the lower rib cage expansion.

To the extent that the diaphragm is the main inspiratory muscle, it would be expected that a marked decrease in its lung-expanding action, as observed during severe ascites, would have a detrimental effect on lung expansion during breathing. Indeed, as ascites was progressively increased, tidal volume and minute ventilation decreased gradually, leading to a prominent increase in arterial P_{CO_2} (Figs. 5 and 6). However, arterial P_{O_2} remained essentially unchanged until ascites was 200 ml/kg. This confirms that the passive inflations performed in our animals were effective in preventing pulmonary atelectasis and, therefore, that the decrease in tidal volume was primarily related to the decrease in the lung-expanding action of the diaphragm, rather than a decrease in pulmonary compliance.

The result of this increased hypercapnic drive was an increase in parasternal intercostal inspiratory activity and, with it, an increase in the inspiratory elevation of the ribs (Figs. 5 and 7). Thus, apparently, the response of the canine respiratory muscle pump to severe ascites is qualitatively similar to its response to diaphragmatic paralysis (8). The diaphragm in our animals, however, was not paralyzed. No attempt was made to record diaphragmatic EMG activity in the present study, because this activity, when recorded with intramuscular electrodes, is well known to show artifactual changes with alterations in the conductivity of the environment surrounding the electrodes (7) or in the length of the muscle fibers (19, 22). However, similar to neural drive to the parasternal intercostals (10, 11), neural drive to the diaphragm is primarily governed by supraspinal control mechanisms, and measurements of motoneuron synchronization in cats by Vaughan and Kirkwood (34) showed that phrenic motoneurons and parasternal intercostal motoneurons receive common monosynaptic inputs. In addition, whereas an isolated increase in parasternal intercostal inspiratory activity would produce a decrease in ΔP_{ab} during inspiration, ΔP_{ab} during inspiration increased with ascites (Fig. 7C). This increase amounted to 70% of the control value; i.e., its magnitude was similar to that observed during isolated stimulation of the phrenic nerves (Fig. 2). It is most likely, therefore, that ascites induced a compensatory increase in neural drive to both the diaphragm and the parasternal intercostals, and the result of this compensation was that the fall in tidal volume, although prominent, was smaller than that anticipated on the basis of the loss of ΔP_{ao} during isolated phrenic nerve stimulation. That is, with an ascites of 200 ml/kg, the fall in ΔP_{ao} (and pleural pressure) during isolated phrenic stimulation was 75% of the control value (Fig. 2), whereas during spontaneous breathing the fall in tidal volume was 48%.

The model of ascites investigated in this study differs from the situation in patients with liver or peritoneal diseases in several respects. 1) The animals were anesthetized, and vagal afferent inputs were suppressed. 2) Pulmonary atelectasis in base of the lung was prevented by repeated lung inflation. 3) Ascites in the animals was produced acutely, whereas in patients it develops slowly over several weeks or months and might, therefore, induce remodeling in the diaphragm and abdominal muscles. Studies on limb muscles in cats and mice (33, 35) and on the diaphragm in hamsters (18, 21) have shown that chronic muscle shortening causes a loss of sarcomeres in series along the muscle fibers. Conversely, when limb muscles in cats and mice are immobilized for a few weeks in a lengthened position, sarcomeres are added (33, 35), and the result is that the length of individual sarcomeres is virtually restored to its initial value. Therefore, it is possible that, in patients with ascites, the increase in passive diaphragmatic and abdominal muscle tension and, with it, the increase in abdominal elastance are partly offset by an addition of sarcomeres. Nonetheless, according to the conventional current theory, dyspnea arises from a mismatch between central respiratory motor activity and incoming afferent information from the chest wall or pulmonary receptors (2, 24). By demonstrating that, in the dog, ascites impairs the lung-expanding action of the diaphragm and induces a compensatory, but insufficient, increase in neural drive to the inspiratory muscles, the present study may account, at least in part, for dyspnea in this condition.

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