Cardiovascular effects of increasing airway pressure in the dog

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POSITIVE END-EXPIRATORY PRESSURE (PEEP) is commonly used to increase arterial oxygenation in patients on ventilators. This primarily occurs through increases in airway distending pressure (static transpulmonary pressure) resulting in increases in lung volume, which serve to open closed airways. This decreases the shunt fraction of cardiac output. One of the limiting factors in the use of PEEP is the decrease in cardiac output (CO) that has been shown to occur in patients (1, 4, 15-17) and experimental animals (13, 24, 28, 29). The mechanism for the change in CO is accepted to be a decrease in venous return (1, 4, 17, 24). Venous return may decrease by one of two mechanisms (3, 8); a) there may be a rise in right atrial pressure which functions as the back pressure to venous return, and b) there may be a change in the peripheral circulation such that venous return decreases at any given right atrial pressure as PEEP is raised. An increase in right atrial pressure could occur in the use of PEEP in one of two ways. First, the rise in pleural pressure that occurs during PEEP could be passively transmitted to the right atrium. Alternatively, increasing pulmonary vascular resistance associated with an increase in lung volume (21, 31) could impose an afterload on the right ventricle which could, in turn, be reflected in an increased right atrial pressure. The difference between the two mechanisms of increasing right atrial pressure would not be readily apparent when measuring pressures relative to atmospheric pressure. However, when measured relative to pleural pressure, right atrial and pulmonary artery pressures would fall as venous return decreased in the first case (passive transmission of pleural pressure) and would rise in the second case (imposed right ventricular afterload). A change in the mechanical properties of the peripheral circulation, i.e., the venous return curve, can be assessed by measuring right atrial pressure (relative to atmospheric pressure) and plotting it against cardiac output (which is equal to venous return in the steady state) as PEEP is increased (3, 8). We decided to investigate the mechanisms by which PEEP may change cardiac output in a preparation that allowed us to vary the degree of lung inflation at any given airway pressure and to measure intracardiac transmural pressure (defined as intracardiac minus pleural pressure) as well as intracardiac absolute pressure (defined as intracardiac pressure relative to atmospheric pressure). In this way the mechanism for a rise in right atrial pressure associated with different degrees of lung inflation during PEEP may be assessed. By plotting cardiac output as a function of absolute right atrial pressure as PEEP is raised, inferences may be made regarding the change in the mechanical properties of the peripheral vascular system, as reflected in the venous return curve.

METHODS

Mongrel dogs of either sex weighing 22-25 kg were anesthetized with sodium pentobarbital (30 mg/kg iv) and then paralyzed with a bolus of 30-60 mg of succinylcholine intravenously; 15- to 30-mg doses of pentobarbital were given every 2 h to maintain adequate anesthesia. A tracheostomy was performed and constant-volume ventilation begun (tidal volume = 300-350 ml). Cannulas were placed in the femoral vein, femoral artery, the right atrium via the left external jugular vein, and the pulmonary artery via the right external jugular vein. The latter had a thermister 3 cm from the distal...
end and an injection port 10 cm from the distal end. With this cannula, pulmonary artery pressure and pulmonary artery wedge pressure were measured, the latter by advancing the catheter a short distance to a wedge position. The wedge pressure was checked by observing the disappearance of the pulmonary artery wave form and by observing the appearance of a different wave form with good respiratory variation. Cardiac output was measured by the thermodilution technique (30). Five milliliters of saline at room temperature were injected into the right atrium and cardiac output calculated from the area under the temperature curve recorded by the thermistor. Cardiac outputs are expressed as percent of the control measured at zero end-expiratory pressure.

A small left thoracotomy was performed in the fourth intercostal space, the pericardium was incised, and a catheter was placed into the left atrial appendage. The thoracotomy incision was closed in three layers to assure an airtight seal. Brass cannulas of 0.25 inch inner diameter were inserted through the chest wall into each hemithorax at the midthoracic level and connected to tubing in common for the measurement of pleural pressure. All vascular pressures were measured relative to the midthoracic level.

The following physiologic parameters were thus measured: airway pressure (Paw), pleural pressure (Ppl), transpulmonary pressure (Ptp = Paw − Ppl), systemic arterial pressure (Part), pulmonary arterial pressure (Ppa), pulmonary artery wedge pressure (Pcw), right atrial pressure (Pra), left atrial pressure (Pla), and cardiac output (CO). Mean pressure over the entire respiratory cycle was obtained by the meaning circuit of the recorder. Mean end-expiratory pressure was taken at one-third the height of the phasic pressure pulse.

In each animal PEEP was raised under two conditions: a) lung volume at FRC was allowed to increase, and b) lung volume changes at FRC were minimized. Condition a was achieved by immersing the expiratory line from respirator under water to the desired level of PEEP. Paw rose more than Ppl at end expiration and, thus, Ptp increased at end expiration. This condition will henceforth be referred to as Ptp increasing. Condition b, above, was achieved by introducing a controlled pneumothorax such that the rise in Ppl matched the rise in Paw at end expiration. This was achieved either by injection of air into the pleural space (three dogs) or by pneumothorax such that the rise in Ppl matched the rise in Paw and Ppl at end expiration and slightly increase Ptp, as will be seen below. Nevertheless, we still refer to this condition at Ptp constant because it was nearly so (see Fig. 1).

An estimate of the change in lung volume that occurred with any change in Ptp was obtained in each animal by constructing a volume-pressure curve at the conclusion of each experiment in which the animal was fully paralyzed by additional injection of succinylcholine. First, a full lung inflation to Ptp = 20 mmHg was given. Then, after return to PEEP = 0, the expiratory line from the respirator was occluded and Ptp was measured as lung volume increased in steps equal to the tidal volume (previously calibrated with a spirometer) given by the respirator. Time was allowed for the lungs to assume quasi-static conditions at each increment of volume.

Control measurements of all variables were taken with the expiratory line open to the atmosphere (PEEP = 0). Then PEEP was raised in four stages to approximately 15 mmHg by immersing the expiratory line under water to varying depths (approximately 5, 10, 15, and 20 cm). Approximately 10 min was allowed at each level of PEEP before measurements were taken. In each dog increments in PEEP were performed under both conditions, the order of the two conditions being randomized. Care was taken to maintain adequate levels of paralysis and anesthesia during the course of the experiment. Experiments were done in two series of animals as follows.

Series 1. In 13 dogs blood volume was maintained constant and CO was allowed to decrease as PEEP was raised. In 5 of these animals increments in PEEP under both conditions were performed before and after bilateral cervical vagotomy. In all of the animals of series 1 CO measurements expressed as percent of control obtained by thermodilution were compared with CO measurements calculated from changes in the arterial-mixed venous O2 difference, which were obtained by measuring arterial and pulmonary artery O2 contents at each level of PEEP and assuming constancy of O2 consumption. No systematic difference could be found between the two methods of measuring changes in CO (expressed as percent of control) and the agreement was within 10%.

Series 2. In six dogs cardiac output was maintained close to control by the infusion of a dextran-blood mixture in 50- to 100-μl increments and checking CO after each infusion. The volume necessary to maintain CO constant under the two different conditions of lung inflation was recorded at each level of PEEP.

Statistical significance was determined generally by analysis of variance. Student's t test for paired variates was used where appropriate and will be specifically indicated as such. All data are shown as the mean ± the standard error of the mean for each point.

RESULTS

Series 1

Transpulmonary pressure, pleural pressure, and lung volume changes. Figure 1 shows the changes in Ptp, Ppl, and the estimated lung volume changes as a function of increasing end-expiratory pressure for both
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conditions, Ptp increasing and Ptp constant. A small increase in Ptp occurred even under the condition of Ptp constant for reasons discussed above. However, both the change in Ptp and the change in lung volume were much less under these conditions than under Ptp increasing conditions. A considerably greater rise in Ppl occurred under conditions of Ptp constant (P < 0.001).

Right heart pressures and cardiac output. Figure 2 shows pulmonary arterial pressure and right atrial pressure (both measured relative to atmospheric) as PEEP was increased. Both pressures rose significantly (P < 0.001) and Pra rose more under Ptp constant conditions than Ptp increasing conditions (P < 0.01). There was no significant difference in Ppa between the two conditions. Cardiac output fell to 38% of control with Ptp increasing, and to 44% of control with Ptp constant conditions. The difference between the two conditions was not statistically significant. Thus, although the change in CO was the same for the two conditions, the Pra was higher at the higher levels of PEEP with Ptp constant conditions. Figure 3 shows the transmural pressures (intracardiac minus pleural pressure) of the pulmonary artery and the right atrium. Note that both Pra and Ppa transmural pressures rose with increasing PEEP under Ptp increasing conditions. Under Ptp constant conditions, however, Pra remained constant and Ppa fell. Thus, right ventricular afterload, when expressed as transmural pressure of the pulmonary artery, increased when lung volume increased despite a decrease in venous return. With a minimal change in lung volume (Ptp constant), the transmural pressure of the pulmonary artery decreased as PEEP was applied.

Left atrial and pulmonary artery wedge pressure. Figure 4 shows pulmonary arterial, left atrial, and pulmonary artery wedge pressures measured at each level of increasing PEEP. Pressures measured at the end of expiration are shown because at end expiration, airway...
pressure is almost equal to alveolar pressure under the conditions of these experiments, which is represented by the line of identity. Under both conditions Ppa and Pcw rose roughly parallel to alveolar pressure. Under Ptp increasing conditions Pcw increased more than Pla, the difference between the two being highly significant (P < 0.001). Under Ptp constant conditions Pla and Pcw rose together and converged rather than diverged at high levels of PEEP.

Although Pla measured relative to atmospheric pressure rose more during Ptp constant conditions than during the Ptp increasing conditions (P < 0.05), the transmural pressures behaved in the opposite fashion. Transmural Pla actually rose slightly (P < 0.025, t test for paired variates at the highest level of PEEP) under Ptp increasing conditions, in spite of a large decrease in cardiac output. Transmural Pla tended to fall under Ptp constant conditions although the decrease was significant only at the second highest level of PEEP (P < 0.05, t test for paired variates).

**Blood pressure.** Part fell under both conditions (from 134 ± 7 to 99 ± 11 mmHg with Ptp increasing and from 129 ± 5 to 86 ± 12 mmHg with Ptp constant; P < 0.01 for both conditions). The fall in Part was proportionally less than the fall in CO. There was no significant difference between the two conditions.

**Effect of vagotomy.** There was no statistically significant change following bilateral cervical vagotomy in the response to PEEP under either of the two conditions in any of the variables. When heart rate was measured, no significant change was found with a rise in PEEP.

**Venous return as a function of Pra.** When venous return is plotted as a function of Pra, a venous return curve is produced (3, 8). Since venous return is equal to cardiac output in a steady state, we have plotted cardiac output as a function of Pra in our studies (Fig. 5). At
equally high levels of Pra, cardiac output is greater for Ptp constant than for Ptp increasing conditions. To compare the difference between the two conditions, curves of CO as a function of absolute Pra were drawn for each dog. When the difference in CO between the two conditions was compared at Pra = 7.5, 10, 12.5, and 15 mmHg, it was found to be statistically significant (P < .05) (t test for paired variates).

**Series II**

**Constant cardiac output.** By transfusion of volume into the animals, cardiac output was maintained close to control as PEEP was increased. As PEEP was raised to the highest level CO fell only to 97 ± 2% of control with Ptp increasing and to 94 ± 4% of control with Ptp constant. The changes in Ptp, Paw, Ppl, and lung volume were similar to those observed in the series I experiments. No significant change occurred in Part.

**Right heart pressures.** Fig. 6 shows absolute and transmural pressures in the right heart as PEEP was increased. Although both Pra and Ppa rose under both conditions, with the rise in Pra being greater with Ptp constant than with Ptp increasing (P < 0.05), a striking difference again emerges in the behavior of the transmural pressures. Transmural Ppa and Pra both rose with Ptp increasing, and both stayed constant with Ptp constant.

**Left atrial and pulmonary artery wedge pressure.** Figure 7 shows measurements of end-expiratory Ppa, Pla, and Pcw at various levels of PEEP. The line of identity which is considered identical to alveolar pressure is also shown. In contrast to the series I experiments, Pla and Pcw rose in a parallel fashion as PEEP increases under both conditions.

**Volume infused.** In the attempt to maintain cardiac output unchanged, a dextran-blood mixture was infused at each level of PEEP as explained above; 736 ± 32 ml were added at the highest level of PEEP with Ptp increasing, and 680 ± 68 ml were added under Ptp constant conditions. The difference was not statistically significant.

Figure 8 shows a plot of the volume infused to maintain constant cardiac output as a function of the change in right atrial pressure. The curves under the two conditions are roughly parallel but the Ptp constant curve is displaced to the right such that for any change in Pra, less volume had to be infused to maintain CO constant with Ptp constant than with Ptp increasing. The change in blood volume was compared in a paired fashion by constructing curves of volume as a function of APra for each dog under each condition. At a APra of 2.5, 5, 7.5, 10, and 12.5 mmHg, the difference between the two
Mechanisms Involved in Changing CO with PEEP

Mechanisms for change in Pra. Right atrial pressure rises with increasing PEEP under both conditions of lung inflation. When end-expiratory lung volume was allowed to increase (Ptp increasing conditions), transmural pulmonary arterial and right atrial pressures rose (Figs. 3 and 6). The increase in pulmonary arterial transmural pressure constitutes an increase in right ventricular afterload. This, in turn, leads to an increase in right ventricular end-diastolic pressure, which is reflected in the observed increase in right atrial transmural pressure. The increase in right ventricular afterload associated with an increase in lung volume may be the consequence of an increase in resistance to pulmonary blood flow seen with lung inflation above FRC (21, 31) or of a rise in back pressure to pulmonary artery flow. Since the rise in absolute right atrial pressure was greater than the rise in transmural right atrial pressure, some of the rise in absolute right atrial pressure is due to transmission of pleural pressure change to the right atrium. When enough volume was infused to keep cardiac output constant, absolute and transmural right atrial and pulmonary artery pressures rose even higher than when cardiac output was allowed to fall. The level to which Pra rises with increasing PEEP will, therefore, depend on the interaction of a change in right ventricular afterload, a change in pleural pressure, and a change in venous return.

At constant lung volume (Ptp constant conditions), pulmonary arterial transmural pressure fell slightly when CO was allowed to fall as PEEP increased (Fig. 3) and remained constant when CO was kept constant by infusion of volume (Fig. 6). This seems to indicate that there was no change in right ventricular function and that changes in right ventricular filling pressures were a function of changes in venous return only under Ptp constant conditions. The level attained by right atrial pressure when Ptp is constant is primarily a function of the pleural pressure, which is passively transmitted to the right atrium. One would also expect transmural right atrial pressure to fall with decreasing CO under Ptp constant conditions as venous return and pulmonary artery transmural pressure fall. It does decrease slightly but not significantly in these studies. We believe that this is due to the fact that the normal right ventricular function curve is such that there may be large changes in flow and ventricular work with only small changes in right ventricular and diastolic and, therefore, right atrial distending pressure. We thus believe that changes in right atrial transmural pressure...
are dominated primarily by changes in pulmonary artery transmural pressure, not by changes in flow in these experiments.

Thus, although changes in absolute right atrial and pulmonary artery pressure with Ptp increasing and Ptp constant are similar, measurements of pleural pressure enable one to differentiate the mechanism by which right atrial pressure rises. The increase in right atrial pressure is determined by the interaction of the increase in pleural pressure and right ventricular afterload in the case of Ptp increasing, and only by an increase in pleural pressure in the case of Ptp constant conditions. Other authors have emphasized the importance of measuring pleural pressure when assessing cardiovascular responses to changing airway pressures (4, 16, 24). The study of Quist et al. (24) most closely approximates our methodology. They showed a decrease in transmural Pra with increasing PEEP. It is not clear from their data what the changes were in Ptp or lung volume and it may be that the changes were small, thus approximating our Ptp constant conditions. If, however, the changes in lung volume and Ptp in their preparation were like our Ptp increasing conditions, then the explanation for the differences between their data and ours is not readily apparent.

Relationships between change in CO and change in Pra. Right atrial pressure functions as the back pressure to venous return (8). A venous return curve is a plot of Pra against venous return, which equals CO in the steady state. As Pra increases, CO decreases. Pra at zero flow is equal to the mean circulatory pressure and the slope of the venous return curve is the conductance to venous return.

In a preparation such as ours, Pra increases with increasing PEEP because Ppl and/or right ventricular afterload increase, as discussed above. If there were no changes in the venous return curve with PEEP, a plot of Pra against CO would inscribe this curve. Figure 5 is a plot of Pra against CO as PEEP is raised. It does not look like a simple venous return curve as obtained in open-chest dogs using a right heart bypass (3, 8). Neither curve is linear and, more importantly, the extrapolated value for Pra at zero flow, which is equal to the mean circulatory pressure, exceeds 20 mmHg. The usual mean circulatory pressure measured with a right heart bypass in anesthetized dogs is in the range of 5-10 mmHg (3, 8). The data in Fig. 5 must mean that the venous return curve shifts to the right as PEEP is applied; that is, there is an increase in the mean circulatory pressure as PEEP increases. If this were not so then, as Pra exceeded the mean circulatory pressure of the control state (presumably less than 10 mmHg), flow would fall to zero. Figure 5 also shows that for any given Pra, venous return is higher when PEEP is applied with Ptp constant than with Ptp increasing.

Figure 9 shows the type of changes in venous return that could occur and yield curves of Pra against flow like our experimental data. A control venous return curve is shown at a PEEP of zero. Venous return curves at two levels of PEEP under both conditions of Ptp are shown. The mean circulatory pressure has increased. The slope of the venous return curve is shown with no change (parallel shift), but the same arguments outlined below would apply as well with a change in slope. As PEEP is increased above control, Pra arises. The point to which venous return, and thus cardiac output, falls is determined by the rise in Pra and the new venous return curve at the higher level of PEEP. Thus, the venous return curve may shift to a higher mean circulatory pressure during rising PEEP and would serve to minimize the decrease in venous return that would be caused by a rising right atrial pressure.

The difference between Ptp constant and Ptp increasing conditions is accounted for by a greater rightward shift in the venous return curve with Ptp constant conditions. This greater shift in the venous return curve with Ptp constant conditions suggests that venous return is inhibited less at each level of Pra. This conclu-
sion is supported by the data in Fig. 8 which shows that at any increase in Pra, less volume had to be infused to maintain CO constant with Ptp constant than with Ptp increasing. The level to which cardiac output falls depends on the interaction between the rise in right atrial pressure and the shift in the venous return curve that occurs during PEEP.

We can only speculate as to the mechanism causing the rightward shift on the venous return curve under isovolumic conditions with PEEP. It could occur because of sympathetic stimulation (3, 8), perhaps mediated through changes in blood pressure and blood flow. A rightward shift in the venous return curve under isovolumic conditions could also occur as the diaphragm descends during PEEP, thus raising intra-abdominal pressure and perhaps shifting blood away from the splanchnic reservoir into the circulation.

The venous return curve seems to shift more to the right with Ptp constant conditions. One might expect a greater increase in intra-abdominal pressure with Ptp constant conditions than with Ptp increasing because with the former, pleural pressure rose more. By means of a saline-filled catheter inserted between intestinal loops through a small abdominal incision we measured the rise in intra-abdominal pressure in two animals during increases in PEEP and indeed found a rise of 5 and 8 mmHg, respectively, under Ptp increasing conditions and 1.3 mmHg in both dogs under Ptp constant conditions. Thus, if a rise in abdominal pressure tends to minimize the decrease in venous return seen with PEEP by shifting the venous return curve to the right, a greater rightward shift with Ptp constant than with Ptp increasing conditions would occur because abdominal pressure rises more with Ptp constant conditions.

Other factors which might play a role in the difference between Ptp increasing and Ptp constant conditions are greater pooling of blood volume in the chest (because of the increased transmural pressures) or the initiation of thoracic inflation reflexes with Ptp increasing conditions. Both of these factors might minimize a rightward shift in the venous return curve with Ptp increasing conditions as compared with Ptp constant conditions.

Changes in Left Atrial Pressure

Figures 4 and 7 show the changes that occurred in absolute and transmural Pla when PEEP was increased under conditions of both decreasing and constant CO. Absolute mean Pla increased under both Ptp increasing and Ptp constant conditions, the increase being higher under Ptp constant conditions. The behavior of the transmural pressures was entirely different. Under Ptp increasing conditions, Pla transmural pressure rose with CO constant and, surprisingly, rose also when CO decreased. With Ptp constant conditions, Pla transmural tended to fall (series I) or remain constant (series II).

The changes in absolute and transmural Pla with Ptp constant are similar to those in absolute and transmural Pra and may be interpreted in a similar fashion. That is, Pla rises with increasing Ppl under Ptp constant conditions. The rise in transmural Pla seen with Ptp increasing is less well understood. In series I, both aortic pressure and cardiac output decreased, which should tend to decrease left ventricular end-diastolic filling pressure and consequently left atrial transmural pressure. Yet, left atrial transmural pressure actually rose. When flow and aortic pressure remained constant (series II), left atrial transmural pressure rose even more with Ptp increasing. The fact that transmural Pla increases with Ptp increasing at constant or decreased cardiac output might indicate that there is a degree of left ventricular dysfunction that occurs as lung volume increases with PEEP. Other workers have reported that when a load is placed in the right ventricle, either by lung inflation (7, 18) or by other means (14, 19, 20), left atrial or left ventricular end-diastolic pressure rises as well as right atrial or right ventricular end-diastolic pressure. The same phenomenon was reported in two patients (16). In addition, some workers (25) have reported that in chronic cor pulmonale left ventricular failure occurs, although others dispute this (18, 26).

We do not know the mechanism that accounts for left ventricular dysfunction with increasing PEEP under conditions of increasing lung volume. Several mechanisms are possible. There may be a decrease in the contractility of the myocardium. This could be caused by vagally mediated reflexes with increasing PEEP (7), changes in coronary flow, and changes in the contractile proteins of the heart (20). In our experiments we found no effect of cutting the vagus nerve, and when PEEP is applied to an isolated denervated heart lung preparation, left ventricular dysfunction also occurs (18). We have no data on the other two possibilities. Alternatively, the contractile properties of the myocardium may be unaltered, but there may be changes in left ventricular geometry that occur during right ventricular overload (2, 14, 19, 27). There could be a shift of the interventricular septum that occurs because of right ventricle dilatation. This could interfere with the function of the left ventricle and be reflected in a rise in left atrial transmural pressure.

Correlation between Pla and Pcw

Intra-alveolar microvasculature is exposed to alveolar pressure and will collapse when the surrounding pressure, represented by the alveolar pressure, exceeds the downstream pressure, which is a function of Pla (22, 23). Then the pressure surrounding the microvasculature exceeds the downstream pressure, i.e., the left atrial pressure minus the hydrostatic difference between the left atrium and the wedge catheter, the wedge pulmonary arterial catheter will record a pressure related to the surrounding, or alveolar, pressure rather than the left atrial pressure. Thus, if alveolar pressure increases more than left atrial pressure, the wedge pulmonary arterial catheter will record changes in alveolar, rather than left atrial pressure. Lozman et al. (16) observed that in patients at levels of PEEP greater than 5 cmH2O there was no correlation between left atrial and wedge pressure, although it is hard to understand why their measurements showed values of Pcw less than Pla at
these levels of PEEP. In open-chest dogs (9) and in baboons (11), Pew and Pla diverge at higher levels of PEEP. All three of these studies were done under conditions similar to our series I Ptp increasing conditions, i.e., lung volume increasing and CO decreasing. Our experiments agree with and extend these observations.

With Ptp increasing Pcw and Pla diverge as PEEP is increased (Fig. 4). Under these circumstances, when we attempted to withdraw arterialized blood from the wedged catheter in a retrograde fashion to fulfill the criteria of Hellem et al. (10) in a few dogs for a satisfactory wedge pressure measurement, we were unable to do so at the higher levels of PEEP. Only when Pla rose in parallel with Pew, i.e., with Ptp constant or CO constant, would these criteria be met. This further demonstrates that there is discontinuity between the left atrium and the wedged pulmonary catheter under conditions of Ptp increasing.

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