Effect of Positive Pressure Breathing on Lung Lymph Flow and Water Content in Sheep

WILLIAM C. WOOLVERTON, KENNETH L. BRIGHAM, AND NORMAN C. STAUB

SUMMARY We studied the effect of 10 cm H₂O of continuous positive airway pressure breathing (CPAPB) on steady state lung fluid balance. In 9 of 20 chronically instrumented, unanesthetized sheep, we measured lung lymph flow, pulmonary vascular pressure, cardiac output, pleural pressure, and lymph and plasma protein concentration during a 2-hour baseline period and 3-4 hours of CPAPB. In eight sheep, we measured the same variables after increasing average left atrial pressure by 18 cm H₂O to cause mild interstitial edema. At the end of the final experiment, we anesthetized the sheep, removed the lungs, and measured their water content. During CPAPB, pleural and left atrial pressures increased by 5 cm H₂O, whereas pulmonary artery pressure increased by 7-10 cm H₂O. Lung lymph flow as well as lymph and plasma protein concentrations did not change significantly. In six sheep, postmortem lung water content was increased above that predicted but was within the predicted range for the group as a whole. We conclude that moderate CPAPB does not measurably affect the steady state lung fluid balance. More important, however, the rise in pulmonary vascular pressure must have been balanced by a rise in perimicrovascular interstitial fluid pressure since filtration did not change. It appears that the fraction of increased alveolar pressure transmitted to the microvessels was via the perimicrovascular fluid rather than through solid tissue contact.

THE IMPROVED arterial blood oxygenation obtained by increasing airway pressure in patients or experimental animals with pulmonary edema is attributed to two mechanisms. The first, and well established one, is by reinfusion of collapsed or fluid-filled alveoli. The second and unsubstantiated one, is by reduction or reversal of transvascular fluid filtration. Drinker and Baker et al. found that positive pressure ventilation markedly increased right lymph duct flow, at least transiently, in anesthetized dogs with acute pulmonary edema.

Several other workers, however, found that positive pressure breathing does not reduce lung water content or the rate of fluid accumulation under edemogenic conditions. Bo and associates have demonstrated that, at constant vascular pressures, in isolated, perfused rabbit lungs increased alveolar pressure and lung volume sometimes increase fluid filtration. They have analyzed the separate effects of the increased alveolar pressure and the increased lung volume.

The importance of having unequivocal data on the effects of positive alveolar pressure in lung fluid balance is important, not only for establishing the rationale for this clinical maneuver, but also because it may aid in establishing the role of interstitial hydrostatic forces which are not directly accessible for measurement.

Net fluid filtration in lung, Qf, in the steady state is governed by the Starling equation, Qf = K(Pmv - Ppmv) - Ko(Pmv - Ppmv), where K is the endothelial fluid conductance, σ is the protein reflection coefficient, P is the hydrostatic pressure, and Π is the protein osmotic pressure in the microvascular (mv) and perimicrovascular (pmv) fluids, respectively.

We used unanesthetized sheep with chronic lung lymph fistulas to determine the effect of continuous positive pressure breathing (CPAPB) on lung lymph flow, lymph protein composition, and postmortem lung water content. Except for transient effects at the onset and offset of CPAPB, in most sheep, lung lymph flow was not altered significantly by 3-4 hours of CPAPB; neither was lung water content markedly affected.

The results confirm and extend those reports indicating that increased alveolar pressure in intact animals does not reduce net fluid flux in the lung and suggesting that perimicrovascular fluid pressure, Ppmv, at the sites of fluid filtration, behaves as if it changes in the direction of alveolar pressure by an amount somewhere between 50% and 90% of the applied airway pressure.

Methods

We anesthetized 20 adult female sheep (33-86 kg) with sodium pentothal (20-30 mg/kg, iv), intubated the trachea with a cuffed endotracheal tube, and maintained anesthesia with 0.5-1.0% fluothane in 50% oxygen, using a positive pressure ventilator. The preparatory operations have been described in detail elsewhere. Briefly, these consisted of a series of three thoracotomies to obtain pure lung lymph from the caudal mediastinal lymph node and to place an inflatable balloon and a catheter in the left atrium, a catheter in the main pulmonary artery, and a catheter attached to a 3- x 4-cm flat balloon in the right pleural cavity at approximately midlung position. We also placed two polyvinyl catheters through a neck incision into the right atrium and ascending aorta by way of the external jugular vein and carotid artery, respectively.

When the sheep had recovered from these operations
and lung lymph was free of blood, we made a chronic tracheostomy. For each experiment, we inserted a 9-mm i.d. cuffed tracheostomy tube (Portex Ltd.). In nine sheep, we successfully completed one or more experiments with lymph flowing. In the remainder, we could not cannulate the lung lymphatic, or else flow through the cannula stopped before any experiments could be done. In these sheep, we waited 1-2 weeks and then did experiments as in the sheep with lymph flowing.

Throughout each experiment, the sheep were unanesthetized and stood quietly in a cage with free access to food and water. They breathed spontaneously. The tracheostomy tube was attached to a three-way connector (22 mm i.d.) through which humidified air flowed (30-40 liters/min) from a tank source into an exhaust line (25 mm i.d.). During baseline studies, the exhaust line opened to the room. During continuous positive pressure breathing, it opened under water at a depth such that the average pressure measured at the external end of the tracheostomy tube equaled 10 cm H2O.

Measurements

We collected lung lymph over 30-minute intervals in heparinized, graduated centrifuge tubes attached to the sheep's flank, but measured lymph flow (Olym) to the nearest 0.1 ml at 15-minute intervals. We obtained blood samples for protein analysis at 60-minute intervals. After centrifugation, we measured total protein concentration in both lymph and blood plasma by the biuret method and of centrifuged homogenate, and heart blood by drying them to constant weight (48 hours at 80°C). We measured the hematocrit of blood and the total hemoglobin of blood and homogenate supernatant fluid by the cyanmethemoglobin method. These procedures are described in detail elsewhere.

We continuously measured pulmonary arterial (Ppa) and left atrial (Pla) pressures, using miniature strain gauges (Micron Instruments, Inc.) connected to a multichannel ultraviolet, direct-writing polygraph (150A, Honeywell Test Instruments Co.). The hydrostatic reference level was the most dependent portion of the lung seen fluoroscopically. To compare our results with data from previous experiments in sheep, we calculated pulmonary arterial (Ppa0, Pla0 and Pmv0).

We also calculated the average hydrostatic pressures over the whole lung based on our determination of the distribution of lung mass in sheep. These pressures are noted by a superscript, ρ, (Ppa, Pla and Pmv).

We completed 17 experiments in 10 sheep with open lung lymph fistulas and 14 experiments in 13 sheep whose external lymph fistulas had closed. Since we observed no differences in any of the other physiological measurements between the two groups, we have combined the results.
All the sheep tolerated the long experiments satisfactorily. They did not appear to be bothered by the continuous positive airway pressure.

In Table 1, we have summarized the effects of our experimental protocols on three steady state measurements of lung mechanics. Pleural pressure was not affected in 18 sheep in which we produced pulmonary venous hypertension by inflating the left atrial balloon, but was increased significantly by about 5 cm H$_2$O during CPAPB; that is, 50% of the applied airway pressure was transmitted to the pleural space. Likewise, FRC did not change measurably when Pla was elevated, but did increase significantly by nearly 1 liter during CPAPB. Lung compliance did not change with any maneuver.

In Table 2, we have summarized the major cardiovascular measurements. In the sheep with normal left atrial pressure (Table 2A), CPAPB increased Ppa in every sheep. Cardiac output was significantly reduced by positive airway pressure breathing. Venous admixture (6.6 ± 6.2%) and arterial blood gas tensions (Pa$_{O_2}$ = 96 ± 7; Paco$_2$ = 37 ± 3) also were not affected by CPAPB.

When we increased Pla by an average of 18 cm H$_2$O (Table 2B), pulmonary artery pressure increased by an average of 12 cm H$_2$O. Cardiac output decreased in 11 of 12 sheep. In the other sheep it did not change. Calculated pulmonary vascular resistance decreased in spite of the fall in cardiac output. On the average, venous admixture (5.1 ± 3.1%) increased slightly (7.4 ± 4.5%), but the change was not statistically significant. The arterial blood gases (Pa$_{O_2}$ = 98 ± 8; Paco$_2$ = 37 ± 3) were not affected.

With the addition of CPAPB, Ppa increased by about 7 cm H$_2$O. Left atrial pressure increased by approximately 5 cm H$_2$O. These vascular pressure changes occurred in every sheep. Cardiac output was significantly reduced relative to the baseline value but was not different from that measured during increased Pla alone. Pulmonary vascular resistance was not significantly altered. Venous admixture and arterial blood gases were not changed.

### Table 1: Effect of CPAPB and Pulmonary Venous Hypertension on Steady State Pleural Pressure, Lung Volume, and Compliance in Unanesthetized Sheep

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Pleural pressure (cm H$_2$O)</th>
<th>Functional residual capacity (liters)</th>
<th>Lung compliance (liters/cm H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Normal left atrial pressure</td>
<td>(13)</td>
<td>(12)</td>
<td>(12)</td>
</tr>
<tr>
<td>1. Baseline</td>
<td>-2.54 ± 1.65†</td>
<td>2.07 ± 0.91</td>
<td>0.17 ± 0.11</td>
</tr>
<tr>
<td>2. CPAPB (10 cm H$_2$O)</td>
<td>+2.42 ± 1.93 ($)</td>
<td>3.02 ± 1.29 (s)</td>
<td>0.16 ± 0.09</td>
</tr>
<tr>
<td>B. Increased left atrial pressure</td>
<td>(18)</td>
<td>(17)</td>
<td>(17)</td>
</tr>
<tr>
<td>1. Baseline</td>
<td>-2.42 ± 1.40</td>
<td>1.82 ± 0.44</td>
<td>0.14 ± 0.05</td>
</tr>
<tr>
<td>2. Increased Pla</td>
<td>-2.58 ± 1.85</td>
<td>1.94 ± 0.49</td>
<td>0.13 ± 0.05</td>
</tr>
<tr>
<td>3. CPAPB (10 cm H$_2$O)</td>
<td>+1.73 ± 2.26 (s)</td>
<td>2.71 ± 0.45 (s)</td>
<td>0.12 ± 0.04</td>
</tr>
</tbody>
</table>

Results are expressed as average ± sd.

* Baseline period for 2 hours, increased left atrial pressure (Pla) alone for 4 hours, CPAPB alone for 4 hours, CPAPB during increased Pla for 3 hours.
† Numbers in parentheses = number of sheep in which measurement was made.
‡ = statistical significance by paired t-test at $P < 0.05$ with respect to value immediately above.

### Table 2: Effect of CPAPB and Pulmonary Venous Hypertension on Steady State Pulmonary Vascular Pressures and Cardiac Output in Unanesthetized Sheep

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Pulmonary artery pressure† (cm H$_2$O)</th>
<th>Left atrial pressure (cm H$_2$O)</th>
<th>Cardiac output (liters/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Normal left atrial pressure</td>
<td>(13)</td>
<td>(13)</td>
<td>(13)</td>
</tr>
<tr>
<td>1. Baseline</td>
<td>29.0 ± 3.0</td>
<td>15.7 ± 3.4</td>
<td>10.3 ± 2.6</td>
</tr>
<tr>
<td>2. CPAPB (10 cm H$_2$O)</td>
<td>39.1 ± 3.8 ($)</td>
<td>25.9 ± 3.6 ($)</td>
<td>15.8 ± 2.6 ($)</td>
</tr>
<tr>
<td>B. Increased left atrial pressure</td>
<td>(18)</td>
<td>(18)</td>
<td>(18)</td>
</tr>
<tr>
<td>1. Baseline</td>
<td>28.1 ± 4.7</td>
<td>15.1 ± 3.8</td>
<td>11.2 ± 2.4</td>
</tr>
<tr>
<td>2. Increased Pla</td>
<td>40.4 ± 7.0 ($)</td>
<td>27.0 ± 7.1 ($)</td>
<td>29.0 ± 5.9 ($)</td>
</tr>
<tr>
<td>3. CPAPB (10 cm H$_2$O)</td>
<td>47.8 ± 7.5 ($)</td>
<td>34.4 ± 7.5 ($)</td>
<td>34.3 ± 6.3 ($)</td>
</tr>
</tbody>
</table>

Results are expressed as average ± sd.

* See Table 1 footnotes for details.
† Pulmonary arterial (Ppa) and left atrial (Pla) pressures measured relative to bottom of lung. Average pulmonary arterial (Ppa) and left atrial (Pla) pressures are integrated up height of lung taking into account the distribution of lung mass (see Staub*).
before applying CPAPB. Table 3 summarizes the data for all 17 experiments with lung lymph flow. In the sheep with normal Pla, the addition of 10 cm H2O continuous positive airway pressure increased Pmv significantly. There is a difference between the calculated value at the bottom of the lung and that integrated over the entire lung. The former, Pmv0, increased by 8 cm H2O, whereas the latter, Pmv, increased by 9 cm H2O. Neither lung lymph flow nor its protein composition was significantly affected. There were transient changes in lymph flow in most sheep at the onset of CPAPB, as in Figure 2.

When Pla was increased, Pmv0 and Pmv increased by 14 and 13 cm H2O, respectively. Lymph flow doubled and there was a significant decrease in the lymph protein concentration as expected.14 When we added CPAPB to the sheep with increased lung fluid filtration, there was a further increase in Pmv averaging 6 cm H2O, but no significant change in lung lymph flow or lymph protein composition.

Figure 3 shows the extravascular lung water per gram of dry blood-free lung (Qwl/dQl), plotted as a function of Pmv in the 20 sheep (7 with lymph flow) killed after 4 hours of CPAPB. These are to be compared with the line and shaded area which represent the hyperbola of best fit and its 95% confidence limits for 20 sheep killed without CPAPB.18 The points show considerable scatter, although most lie within the predicted range. Six have high water content and one is low. Overall, the sheep with CPAPB appear to have about the same water content as those without added airway pressure at a given microvascular pressure.

Discussion

We studied lung fluid balance in sheep for several hours in response to moderate elevations of Pla and airway pressure. Since these sheep had normal lungs, the situation is not identical to that of patients with various forms of adult respiratory distress syndrome.1,3,7 Also, they were breathing spontaneously rather than being ventilated mechanically.

Baseline lung compliance was similar to that in other
TABLE 3  Effect of CPAPB and Pulmonary Venous Hypertension on Steady State Lung Lymph Flow and Lymph and Plasma Protein Composition in Unanesthetized Sheep

<table>
<thead>
<tr>
<th>Conditions*</th>
<th>Pulmonary microvascular pressure† (cm H₂O)</th>
<th>Lung lymph flow (ml/hr)</th>
<th>Lymph Proteins</th>
<th>Plasma Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pmv₀</td>
<td>Pmv</td>
<td></td>
<td>TP (g/100 ml)</td>
</tr>
<tr>
<td>A. Normal left atrial pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Baseline</td>
<td>17.9±2.4</td>
<td>6.5±1.8</td>
<td>8.2±3.2</td>
<td>4.12±0.28</td>
</tr>
<tr>
<td>2. CPAPB (10 cm H₂O)</td>
<td>25.9±2.7</td>
<td>15.6±1.6</td>
<td>7.7±4.1</td>
<td>3.91±0.43</td>
</tr>
<tr>
<td>B. Increased left atrial pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Baseline</td>
<td>18.2±2.5</td>
<td>6.3±1.8</td>
<td>6.7±2.1</td>
<td>4.19±0.48</td>
</tr>
<tr>
<td>2. Increased Pla</td>
<td>32.3±3.1</td>
<td>19.5±3.3</td>
<td>14.7±3.8</td>
<td>3.03±0.82</td>
</tr>
<tr>
<td>3. CPAPB (10 cm H₂O)</td>
<td>38.4±3.1</td>
<td>25.7±3.1</td>
<td>12.5±4.2</td>
<td>3.02±0.69</td>
</tr>
</tbody>
</table>

Results are expressed as average ± SD. TP = total proteins; A(%) = albumin fraction.

* See Table 1, footnotes, for details.
† Pulmonary microvascular pressure (Pmv₀) calculated for zone II and III conditions, by the formula of Staub:19 subcript„ relative to bottom of lung; superscript„, integrated value over entire lung.

mammals on a body weight basis.35 It was not significantly altered by elevation of Pla. Modest lung stiffening (compliance decreased 20-25%) with pulmonary vascular congestion has been reported in dogs,28 in cats,29 and in rabbits.30 Our method of measurement may have been too crude to detect such a small decrement.

The pulmonary vascular bed of unanesthetized sheep is normally well filled with blood. Because of the spatial distribution of lung mass,24 about 80% of the lung is in zone III (see example in Table 4 of reference 19). Under these conditions, increases in pulmonary vascular distending pressures may not cause further lung stiffening.

During CPAPB, about half of the applied airway pressure was transmitted to the pleural balloon and to the left atrium. The similarity of the changes at the two measuring sites suggests that the measurements are reliable even though the sheep had had prior thoracic operations.

Again, we detected no significant changes in lung compliance with the application of CPAPB. These results are similar to those reported in dogs by Lenfant and associates.31

When left atrial pressure was normal, the pulmonary artery pressure increased by an amount equal to the increment in airway pressure (10 cm H₂O), whereas Pla increased only 5 cm H₂O. The pressure difference, Ppa-Pla, increased. This is reasonable because the zone II/III boundary moved down the lung approximately 5 cm, placing more of the lung (50%) into zone II. The net effect is to increase the pulmonary vascular resistance.

In the presence of increased left atrial pressure, however, the applied airway pressure was not transmitted fully to the pulmonary artery. This seems reasonable since the lung remained fully in zone III because of the high left atrial pressure. This is further supported by the fact that the pulmonary vascular resistance scarcely changed.

We have included calculations of pulmonary microvascular pressure at the bottom, Pmv₀, and integrated over the entire lung, Pmv, using our data on the spatial distribution of lung mass, estimates of the distribution of pre- and postmicrovascular resistance, and formulas for calculating Pmv in lung zones II and III.19 We are unable to measure the microvascular pressure directly. The reason we have included the numbers is that they provide a basis for comparing lung water content between these sheep and those on which we previously reported.18

Plasma and Lymph Protein Composition

The plasma and lymph total protein concentrations and their electrophoretic composition (albumin fraction) during the baseline and increased left atrial pressure experiments are similar to those we have reported previously for unanesthetized sheep.18,22 That there was no change in lymph protein concentration or its albumin fraction during CPAPB can only mean that the factor, Kₒ(Tlv-Tplmv), in the fluid transport equation remained constant. We therefore have only to consider the hydrostatic driving pressure (Pmv-Pplmv) in relation to net fluid filtration.
**Lung Lymph flow**

Lymph flow transients at the onset of positive airway pressure were present in several sheep (not in the sheep represented in Figure 1) and were small in magnitude. When they occurred, they were consistent with net fluid accumulation in the lung during CPAPB. Since about half of the applied airway pressure was transmitted to the pleural space, it is likely that this elevated pressure compressed lymphatics as they passed over the pleural surface of the lung and from the lung hilum toward the junction of the great veins in the neck. This Starling resistor effect would decrease lymph flow until the lymph driving pressure could rise sufficiently to overcome the compression. Indeed, we have recorded pressure as high as 14 cm H₂O in the main lung lymphatic when it was obstructed.

The amount of fluid retained was not large, of the order of several milliliters. However, we believe it represents a volume larger than the capacity of the lymph vessels themselves. In other words, the retained fluid probably would be in the loose connective tissue septae and peribronchovascular spaces. The volume so retained represents less than a 2% change in lung water; this is too little to be detected histologically or by lung water content measurements. Ba and associates found that increasing lung volume at constant vascular and alveolar pressures (by lowering Ppl) increased fluid filtration in isolated perfused rabbit lungs. This can be interpreted as indicating a fall in fluid pressure in the loose peribronchovascular (extraalveolar) connective tissue with consequent increased storage capacity for interstitial fluid.

The most important result of our study is what happened to steady state lung lymph flow (that is, fluid filtration, Qf). It did not change, either when left atrial pressure was normal or when it was elevated.

Before interpreting the data further, let us examine steady state lung lymph flow as a sensitive measure of net filtration forces. Within the range of microvascular pressures we have studied, every rise in Pmv brought a rise in lung lymph flow; the increased flow was approximately linear with the increasing pressure.

In the data shown in Table 3, the increase in Pmv, when Pla was increased, averaged 13 cm H₂O, and lung lymph flow increased 8 ml/hr. Thus, lymph flow in these sheep increased by 0.5 ml/hr for every 1 cm H₂O rise in Pmv, as in our previously reported results. We doubt that we could detect such a small increment in a single animal because of spontaneous variations in lung lymph flow. However, we do believe we could detect a Pmv rise of 2 cm H₂O; that is, an increase of 1 ml/hr in lymph flow. Among a group of sheep, the detection of small rises in filtration pressure may be even more sensitive.

**Lung Water Content**

Figure 3 shows that the lung water content as related to pulmonary microvascular pressure was not significantly different on the average in the sheep with CPAPB than for those without that intervention. At least two of the 20 animals had distinctly elevated lung water contents and four more were just outside the 95% confidence limits. One had a water content less than predicted.

There are problems here concerning lung water content changes (as there have been in other experiments on positive pressure breathing). In the first place, the exact placement of the individual points depends on how microvascular pressure is calculated, since it cannot be measured directly. It would be better to plot lung water against the sum of pressures in the Starling equation. However, that requires an assumption about both the absolute value and change in Ppmv. In the second place, some fluid did accumulate during the transient period at the onset of CPAPB in most sheep (see Fig. 2, for example). However, small increases are not to be equated with the steady state. One can argue from the transients and the trend toward higher lung water among all of the points in Figure 3 (14/20 points are above the regression hyperbola) that lung water actually was increased by the positive pressure breathing. That is certainly in keeping with results of Demling and others, but a strict comparison between brief experiments in isolated lung lobes and our unanesthetized, steady state sheep preparation is questionable. Even in the experiments of Demling and associates, which lasted 2 hours, the increase in lung water content was quite modest.

The most conservative conclusion we can make is that positive pressure breathing for 3-4 hours at 10 cm H₂O did not decrease lung water.

**Physiological Role of Positive Airway Pressure in Lung Fluid Balance**

We realize the limitations in using intact, unanesthetized animals for our experiments, but we accepted these because we wanted to make measurements of steady state lung lymph flow and its protein content. Thus, we have restricted our interpretation of the physiological role of positive pressure breathing to a lumped parameter system; that is, we have assumed a uniform microvascular-perimicrovascular model for fluid exchange.

Since the protein composition of plasma and lymph was not affected by CPAPB, the only reasonable conclusion is that, whatever positive pressure did to vascular hydrostatic pressure, it had an equal effect on perimicrovascular interstitial hydrostatic pressure (Ppmv). If such a relationship is correct, it suggests that the main filtration site is indeed within the alveolar walls in vessels that are exposed to alveolar pressure, rather than in large vessels within the loose connective structures of septae and airways whose perivascular hydrostatic pressure is believed to decrease relative to alveolar pressure during lung expansion.

It also suggests that there is not sufficient solid tissue strength to allow transmission of alveolar surface pressure to the vascular surfaces independent of the intervening tissue fluid, as has been theorized by Guyton et al. It is possible to construct an alternative hypothesis of equal and opposite factors that could explain the absence of steady state lymph flow changes either in the presence of normal left atrial pressure or with elevated left atrial pressure, but it is very difficult to conceive of the same explanation working in both those situations. For exam-
ple, it could be argued that, under conditions of normal left atrial pressure, CPAPB acted to increase the hydrostatic driving pressure between the vascular compartment and the perivascular interstitial space but at the same time acted to decrease the surface area for fluid filtration by compressing blood vessels. This is so because the boundary between lung zones II and III moved down the lung 5 cm and vascular resistance increased. Obviously, some compression of the microvessels occurred, but how does this explanation operate when left atrial pressure was high so that the microvessels were not compressed? All of the lung remained in zone III, and vascular resistance did not change significantly.

Another possibility is that in some way the filtration coefficient, that is, the actual fluid conductance (K) of the microvascular endothelium, is altered so as to produce "pore constriction" when alveolar pressure rises. However, this is extremely unlikely, because we have shown elsewhere that large rises in microvascular pressure in the lung apparently do not cause any changes in pore configuration.34 Besides, we detected no changes in lymph protein composition.

One could argue that, when CPAPB was applied in sheep with normal left atrial pressure there was no direct pressure transmission to the perimicrovascular fluid. Rather, a small amount of fluid accumulated in the alveolar wall interstitium and raised the fluid pressure there sufficiently to decrease the filtration pressure back to its pre-CPAPB level. The net result would be no increase in steady state lymph flow. If one accepts the interstitial pressure-volume relationships postulated by Guyton,36 then a small amount of fluid accumulation could cause this effect. The accumulation would be too small to be detected by our analysis of lung water content. However, this explanation does not hold when left atrial pressure is high and interstitial fluid volume is already expanded by 10% or 25%. Under those conditions, the perimicrovascular interstitial fluid pressure should already be increased to be equal to surface pressure, that is, alveolar pressure. Perhaps it is a small point, since the net result is the same in either case. However, it requires two different explanations for the experiments, instead of one.

The only reasonable explanation we can make based on all of the data (with and without expansion of the lung's interstitial fluid volume) is that equal increments of applied airway pressure are transmitted to the microvascular lumen and to the perimicrovascular interstitial fluid. Thus, in our experiments on whole animals, we conclude that whatever the absolute value of average perimicrovascular interstitial fluid pressure (Ppmv) may be, it acts as if it were increased by an amount equal to at least 50% (ΔPia) of the applied airway pressure.

Role of CPAPB in Clinical Pulmonary Edema

We confirm the findings of Demling et al.,13 Hopewell and Murray,13 Iliff,14 and Wagner et al.15 that continuous positive airway pressure does not significantly influence fluid filtration in the normal lung and does not act to expedite the removal of excess extravascular fluid. It seems that the confirmed benefits of positive airway pressure in acute pulmonary edema are its ability to reinflate and ventilate fluid-filled or collapsed alveoli and to force fluid and foam bubbling up in the central airways more peripherally, thereby improving airways function.

References

29. Frank, NR: Influence of acute pulmonary vascular congestion on

**Regulation of Cardiac Output by Stroke Volume and Heart Rate in Conscious Dogs**

**Stephen F. Vatner and Dedo H. Boettcher**

**SUMMARY** We examined the relative importance of increases in stroke volume and heart rate in mediating increases in cardiac output in response to elevations in preload, inotropic state, or a combination of these factors in 15 conscious dogs with low, physiological heart rates. Elevating preload by volume loading with saline increased left atrial pressure by 15 mm Hg, cardiac output by 147 ± 7% from a control of 2340 ± 80 ml/min, and heart rate by 143 ± 7% from a control of 62 ± 2 beats/min, but did not alter stroke volume. Similarly, volume loading with blood increased cardiac output by 100 ± 5% and heart rate by 108 ± 10%, while stroke volume did not change significantly. Hemorrhage in conscious dogs reduced cardiac output by 49 ± 4% and stroke volume by 75 ± 2% while increasing heart rate by 113 ± 15%. In dogs anesthetized with pentobarbital Na, and with an open chest, volume loading increased stroke volume by 243 ± 89% but did not alter heart rate. In conscious dogs, isoproterenol increased cardiac output solely by increasing heart rate, failing to increase stroke volume, whereas dobutamine, a sympathomimetic amine with less positive chronotropic action than isoproterenol, raised stroke volume by approximately 25%. Infusion of both sympathomimetic amines in the volume-loaded state increased stroke volume by a slightly greater amount than either volume loading or sympathomimetic amine infusion by itself. Severe exercise also increased stroke volume by 27 ± 2%, whereas cardiac output rose by 402 ± 24%. Thus, in the conscious dog with a low physiological heart rate, stroke volume is relatively large at rest and does not increase at all, even with maximal tolerated volume loading, and only modest increases were observed with exercise or combined sympathomimetic amine infusion and volume loading.

Whereas it is obvious that the cardiac pump can increase its output only through a change in frequency or a change in stroke volume, the relative importance of these two factors in mediating changes in preload remains controversial despite intense investigation of this subject during the past century. Starling’s pioneering work on the heart-lung preparation established a dominant role for stroke volume in mediating changes in cardiac output.¹

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Rushmer, using a normal conscious animal model,² ³ challenged the views of Starling and concluded that stroke volume remained roughly constant, particularly when cardiac output rose during exercise.² However, Rushmer and colleagues did not examine the effects on stroke volume of elevating preload by volume loading, a case in which a large rise in stroke volume might be predicted.

The goal of this study was to determine the extent to which stroke volume changed in response to marked alterations in preload, starting from the basal state, i.e., a reclining conscious dog with a physiological heart rate. It was considered essential to study animals with low, physiological heart rates, since the importance of changes in stroke volume tend to be overemphasized when the baseline heart rate is elevated, as occurs in excited animals, or during general anesthesia. To examine responses to marked changes in preload, trained dogs instrumented with electromagnetic flow probes on the aorta were studied when cardiac output was elevated by increasing preload to the maximum tolerated by the conscious dogs and when cardiac output was reduced by diminishing preload.
Effect of positive pressure breathing on lung lymph flow and water content in sheep.

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