The potential for significant interaction between PEEP and the peripheral microcirculations is not as well appreciated as are its central circulatory effects. Therefore, we studied the effects of PEEP, 15 mm Hg, on microvascular fluid flux in the hindlimb of ten mature sheep. Changes in prefemoral lymph flow (Ql) and in lymph to plasma (L/P) total protein (TP) ratios were measured following the application of PEEP for 2 h, before and during hyperdynamic sepsis. Sepsis was induced by cecal ligation and perforation (CLP). Although the onset of sepsis was not associated with an increase in prefemoral Ql, the [L/P] ratio of iodinated 125I human serum albumin ([125I]-HSA) was significantly greater 72 h after CLP than during the nonseptic baseline study. Histologic examination of gastrocnemius muscle also demonstrated an increase in protein-rich interstitial edema during the septic studies. During the 2 h of PEEP, prefemoral Ql increased equally (p<0.05) in three study periods: (1) baseline nonseptic, ΔQl = + 1.2 ± 1.4 ml/h; (2) septic period 1, 24 to 48 h after CLP, ΔQl = + 1.3 ± 1.2 ml/h; and, (3) septic period 2, 72 h after CLP, ΔQl = 1.0 ± 0.6 ml/h. Calculated microvascular hydrostatic pressures also rose significantly during PEEP therapy in all three study periods. We conclude that PEEP, 15 mm Hg, increased hindlimb microvascular fluid flux and may thereby increase interstitial fluid content in tissues drained by the prefemoral lymph node. These effects of PEEP were not aggravated by hyperdynamic sepsis, despite a presumed increase in systemic microvascular permeability at this time.

(Chest 1989; 96:1142-49)

**Material and Methods**

**Experimental Preparation**

A complete description of the model has been previously published.** After a five- to seven-day period of acclimatization in our laboratory, we studied ten mature Suffolk sheep weighing 30 to 40 kg (9.0 to 11.4 lb) body, BSA. Before initial preparatory surgery, solid food was withheld, and a combination of penicillin (1×107 units) and streptomycin (1.25×106 mg) was administered IM every
12 h. The sheep were intubated and anesthetized (halothane, 1.5 to 2 percent, and oxygen, 5 to 6 L/min). The efferent duct of a prefemoral lymph node was cannulated with a nonheparinized Silastic catheter (medical grade tubing, 0.06 cm ID × 0.12 cm OD; Dow Corning) as described by Demling et al.14 with modifications described by our laboratory.15 In sheep, prefemoral lymph originates from skin, subcutaneous tissue, and superficial muscles of the posterior thorax, lateral abdomen, pelvis, and thigh.11,12 An SF catheter introducer sheath (Cordis 501-606; Cordis Laboratories Inc) was then inserted into the external jugular vein, while the aorta was cannulated through the right carotid artery with a nonheparinized Silastic catheter (medical grade tubing, 0.32 cm OD; Dow Corning). The femoral artery and vein were also cannulated on the side contralateral to lymph cannulation. Central catheters were flushed throughout the study with 5 percent dextrose in water containing 1,000 units of heparin/1,000 ml. at 1.0 ml/h. Peripheral lines were maintained as “heparin locks.” Finally, a tracheostomy was performed. A size 10, low-pressure cuffed tracheostomy tube (Shiley, Pfizer Corp) was inserted between two adjacent tracheal rings approximately 10 cm below the larynx. The tracheostomy tube was attached to a three-way connector (22 mm ID) through which humidified air flowed. Following recovery from anesthesia, food and water were provided ad lib. Ringer’s lactate solution, 50 to 100 ml/kg/day, was administered to ensure adequate hydration prior to the experiments.

Once steady-state lymph flow (Qt) was evident, usually 72 to 96 h following preparatory surgery, baseline studies were performed in the unanesthetized state. At this time, a thermistor-diffusion right heart catheter (Edwards Laboratories) was flow-directed into the pulmonary artery. During the baseline, ie, nonseptic study, prefemoral Qt was measured for a 4-h zero-PEEP (ZEEP) study period. The effect of 15 mm Hg of PEEP on prefemoral Qt was then monitored for a 2-h period. PEEP was applied with an Ambu-20 PEEP valve (21-3000, Narcoscientific, Denmark) attached to the expiratory end of tubing connected to the tracheostomy tube; high flow air through a reservoir bag and a humidifier was provided on the other end of the tubing. To ensure a closed system, the external end of the tracheostomy tube was connected to a pressure monitor.

After the baseline PEEP study, an intra-abdominal source of bacterial sepsis was created by cecal ligation and perforation (CLP) as previously described.16 Postoperatively, animals were allowed free access to food and water, and the rate of Ringer’s lactate solution infusion was increased from 150 to 250 ml/kg/day to maintain the pulmonary arterial occlusion pressure (PAoP) at preseptic levels. Study animals were monitored every 6 to 8 h. The onset of hyperdynamic sepsis was arbitrarily defined when the CO rose by 25 percent and the systemic resistance fell despite an unchanged mean blood pressure. This period usually occurred between 24 and 48 h after CLP. It has been demonstrated in our laboratory to be temporally associated with significant injury in both the pulmonary17 and systemic18 microcirculations. The ZEEP and 15 mm Hg PEEP studies were then repeated in ten sheep in the awake state (period septic 1), as described for the nonseptic study period. Five sheep were subsequently monitored for an additional 24 to 48 h, ie, 48 to 72 h after CLP when ZEEP and 15 mm Hg PEEP studies were repeated (period septic 2).

This protocol was approved by the University of Western Ontario Committee governing the experimentation of animals. Mepheridine was administered in each postoperative period to lessen any discomfort from the preparation surgery and subsequent laparotomy. Mepheridine was also used to minimize any stress during the application of PEEP when clinically apparent.

### Specific Measurements and Calculations

Peripheral lymph samples were collected in graduated, heparinized tubes according to the prescribed timetable (Fig 1). Lymph quantity was recorded every 15 min, expressed as ml/60 min, and then averaged for each study period. From pooled lymph, the total protein and albumin concentration (g/dl) was measured by the biuret method,16 using an automated system (Auto Analyzer, Technicon Instruments); duplicate samples differed by less than 5 percent. We also measured the flux of radioiodinated albumin from blood to lymph during the three study periods in four sheep. Ninety minutes before completion of the ZEEP study, we injected 185 KBq of a commercial preparation of human serum albumin (HSA, Frosst Laboratories) tagged with 125I through the proximal port of the right heart catheter. Baseline blood and lymph were sampled prior to the injection, and at the end of each 15-min period for the last 90 min of the ZEEP study. One milliliter of lymph, or the total amount if volumes were less than 1 ml, and 1 ml of plasma were counted in a gamma scintillation counter and standardized to 10% HSA counts/min/ml (cpm). The lymph to plasma ratio of the cpm ([L/P] = 10% HSA) was calculated and averaged.

With lymph collection, blood was obtained from the carotid arterial line for measurement of total protein and albumin concentration (g/dl), hemoglobin, hematocrit, and total WBC count. The hemoglobin ([Hb] g/dl) and total WBC count (per cu mm) were measured by a Coulter cell counter (model ZF) and the hematocrit (Hct, %) was measured in triplicate with a microhematocrit centrifuge. With appropriate temperature corrections, oxygen (PO2), (mm Hg) and carbon dioxide (PCO2), (mm Hg) tensions and pH were determined (AME-1 blood gas analyzer, Radiometer) from central arterial (ie, PaO2), mixed venous (ie, PaO2), and femoral venous blood drawn from the carotid arterial line, the distal lumen of the right heart catheter, and the femoral venous catheter, respectively. Saturation were calculated from the pH and PO2 using dissociation curves for sheep blood.17

<table>
<thead>
<tr>
<th>STUDY PROTOCOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparatory Surgery</td>
</tr>
<tr>
<td>72-96 hrs recovery and Qt stabilization</td>
</tr>
</tbody>
</table>

![Diagram of study protocol](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21603/)

**FIGURE 1.** Study protocol to define the effects of PEEP on peripheral lymph flow (Qt) in nonseptic and septic sheep. CLP = cecal ligation and perforation; H = hemodynamic measurements; B = blood sampling; L = lymph collection every 15 min.

With lymph collection, blood was obtained from the carotid arterial line for measurement of total protein and albumin concentration (g/dl), hemoglobin, hematocrit, and total WBC count. The hemoglobin ([Hb] g/dl) and total WBC count (per cu mm) were measured by a Coulter cell counter (model ZF) and the hematocrit (Hct, %) was measured in triplicate with a microhematocrit centrifuge. With appropriate temperature corrections, oxygen (PO2), (mm Hg) and carbon dioxide (PCO2), (mm Hg) tensions and pH were determined (AME-1 blood gas analyzer, Radiometer) from central arterial (ie, PaO2), mixed venous (ie, PaO2), and femoral venous blood drawn from the carotid arterial line, the distal lumen of the right heart catheter, and the femoral venous catheter, respectively. Saturation were calculated from the pH and PO2 using dissociation curves for sheep blood.17

Systemic (systolic, BP; diastolic, BPd; mean, BP) pulmonary (systolic, PAs); diastolic; PAd; mean (PAP), PAOP, and central venous (CVP) pressures were measured with an arteriovenous pressure transducer and a digital display with continuous paper recording system (Hewlett-Packard arterial/venous pressure module, model 78205B). Transducers were leveled to the humeral tuberosity which was taken as the level of the right atrium in sheep. Cardiac output (CO; L/min) was determined in triplicate by the thermodilution technique with a portable computer (model 9520; Edwards Laboratories), using 10 ml of iced saline solution, averaged, and subsequently indexed (CI) for BSA. In sheep, BSA is calculated as: 70 × weight in kg17/1,000.16

Plasma (πp) and lymph (πL) colloid osmotic pressures were
Table 1—The Effect of PEEP and Sepsis on Measured and Calculated Flow and O₂ Delivery Related Variables During the Three Study Periods

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-septic Study</th>
<th>Septic Study 1</th>
<th>Septic Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Flow-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>117 ± 14</td>
<td>118 ± 15</td>
<td>122 ± 13</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>22.8 ± 3.0</td>
<td>39.6 ± 4.6*</td>
<td>24.3 ± 4.2</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>5.4 ± 0.9</td>
<td>5.3 ± 0.9</td>
<td>7.3 ± 1.5†</td>
</tr>
<tr>
<td>SVI, ml/beat/m²</td>
<td>77 ± 11</td>
<td>57 ± 14*</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>HR, beat/min</td>
<td>71 ± 15</td>
<td>96 ± 20*</td>
<td>97 ± 14†</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>12.8 ± 2</td>
<td>23.1 ± 3*</td>
<td>12.7 ± 2</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>8.1 ± 3</td>
<td>14.8 ± 3*</td>
<td>9.6 ± 5</td>
</tr>
<tr>
<td>SVRI, dyne·sec/m²</td>
<td>1652 ± 220</td>
<td>1611 ± 291</td>
<td>1256 ± 171†</td>
</tr>
</tbody>
</table>

* p<0.05 compared with PEEP = 0 during the same study period.
† p<0.05 compared with nonseptic value, at the same PEEP level.
‡ p<0.05 compared with the septic value at the same PEEP level.

PEEP increases Non-pulmonary Microvascular Fluid Flux (Hersch et al)

**Results**

Blood cultures obtained with definition of the study septic period demonstrated a polymicrobial bacteremia in all sheep. With completion of the experiment, postmortem examination revealed an inflammatory mass in the right lower quadrant together with abdominal distention due to distended loops of bowel and ascietes.

During the septic study, the mean CI was elevated from baseline study (change [Δ], sepsis minus baseline; ΔCI = +1.9 ± 1.1, L/min/m², p<0.05), while the mean BP was unchanged and the SVRI was depressed (ΔSVRI = 396 ± 195 dyne·sec·cm⁻²·m², p<0.05 vs baseline) (Table 1). The mean CI progressively increased throughout the septic 2 study (ΔCI = +3.9 ± 1.4 L/min/m²; p<0.05 vs baseline) without any concurrent change in the mean BP. In both septic studies, the increase in CI was due to an increase in HR (septic 1 and 2 studies, ΔHR = +26 ± 18 and +52 ± 14 beats/min, respectively; p<0.05), since the mean SVI was unchanged between baseline and both septic 1 and 2 studies (ΔSVI = −1 ± 16 and −1 ± 15 ml/h/m², respectively; p = NS). Finally, O₂E and HO₂E were lower while both systemic O₂d and VO₂ were greater during the septic studies than during the baseline study (Table 1).

Sections of the gastrocnemius muscle were normal at baseline. During the septic study periods, albumin-rich intercellular edema was diffusely evident in all

Calculated using the equation of Navar, corrected for the albumin/globulin ratio. Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), stroke volume (SV), systemic O₂ consumption (VO₂), systemic O₂ delivery (SO₂d), and O₂ extractions of whole body (O₂E) and hindlimb (HO₂E) were calculated by standard formula and indexed for BSA where appropriate. Mean capillary hydrostatic pressure within the peripheral microcirculation (PC) was calculated by the formula: PC = 0.2 (BP-CVP) + CVP, which assumes that 80 percent of the vascular resistance is on the arterial side of the peripheral microcirculation. We approximated net forces favoring increased transmucosal fluid flux by calculating the following relationship: (PC-[pH-nil]). From lymph flow (QL, ml/min) and lymph to plasma total protein ([L]/[P]TP) ratios, we calculated the clearance of lymph total protein (CLyr) as: QL×[L]/[P]TP (ml/min). Finally, relative changes in plasma volume during PEEP ventilation were approximated during each study using the measured values of Hg and Hct.

Biopsy specimens from the gastrocnemius muscle, on the side opposite the lymph cannulation, were also taken during each study period in three animals. Samples were obtained using general anesthesia before CLP and at completion of the study periods immediately before euthanasia. Specimens were fixed in 10 percent formalin for light microscopy and processed by the usual paraffin-embedding technique. All sections were stained with hematoxylin and eosin and colloidal iron, the latter to identify the presence of albumin in the extracellular space.

**Statistics**

Data are expressed as the mean ± SD. Two-way analysis of variance (ANOVA) with repeated measures was used to examine the PEEP effect, the septic effect, and the PEEP by sepsis interaction (ie, the differential effect of PEEP). [L]/[P] TP/HSA ratios were analyzed by ANOVA with repeated measures, and the three study periods were compared by the Tukey's HSD test. Significance was considered at p<0.05.
specimens and was considered greater in intensity during the septic 2 than septic 1 study (Fig 2). However, prefemoral Qt value was not significantly different between the baseline study and either of the septic 1 or septic 2 studies (Table 2). Although the [L/P]TP ratios were lower than measured at baseline during the septic 2 study, the [L/P] ratio of 125I-HSA was significantly greater during this study period than during baseline study (Fig 3).

PEEP's Effect on Hemodynamics (Table 1)

With the addition of PEEP, the study animals did not appear uncomfortable, and their spontaneous respiratory rate did not increase significantly. The mean SVI fell during PEEP, 15 mm Hg, in all study periods (Table 1), although this depression was lower in the septic 2 study (ΔSVI = -13 ± 8 ml/h/m²; p<0.05) than in either of the baseline (ΔSVI = -25 ± 16 ml/h/m²) or septic 1 (ΔSVI = -38 ± 27 ml/h/m²) studies. During all study periods, an increase in the mean HR prevented a significant depression in the mean CI. The measured CVP, PAP, and PAOP rose similarly in all periods during PEEP. PEEP did not alter any of the mean PaO₂, systemic O₂d, VO₂, O₂E.

Table 2—The Effect of PEEP and Sepsis on Lymph- and Blood Volume-related Variables During the Three Study Periods

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonseptic Study</th>
<th>Septic Study 1</th>
<th>Septic Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(n = 10)</td>
<td>(n = 5)</td>
</tr>
<tr>
<td>Lymph flow-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qt, ml/60 min</td>
<td>4.2 ± 1.8</td>
<td>5.4 ± 2.4*</td>
<td>4.9 ± 2.2</td>
</tr>
<tr>
<td>[L/P]TP ratio</td>
<td>0.56 ± 0.06</td>
<td>0.47 ± 0.08*</td>
<td>0.52 ± 0.08*</td>
</tr>
<tr>
<td>CTP, ml/60 min, mm Hg</td>
<td>2.3 ± 0.9</td>
<td>2.5 ± 1.2</td>
<td>2.5 ± 1.3</td>
</tr>
<tr>
<td>Pco, mm Hg</td>
<td>29.9 ± 4.2</td>
<td>35.6 ± 5.0*</td>
<td>32.2 ± 6.3</td>
</tr>
<tr>
<td>Serum total protein, mg/ml</td>
<td>58.2 ± 2.8</td>
<td>57.6 ± 3.8</td>
<td>49.3 ± 4.9†</td>
</tr>
<tr>
<td>npr, mm Hg</td>
<td>19.4 ± 1.4</td>
<td>19.2 ± 1.8</td>
<td>15.4 ± 2†</td>
</tr>
<tr>
<td>npi, mm Hg</td>
<td>8.9 ± 1.5</td>
<td>7.5 ± 1.2*</td>
<td>6.6 ± 1.6*</td>
</tr>
<tr>
<td>[Pc-(np-rpi)], mm Hg</td>
<td>19.4 ± 3.8</td>
<td>23.8 ± 3.5*</td>
<td>23.4 ± 6.6†</td>
</tr>
<tr>
<td>Blood Volume-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hct, %</td>
<td>28.4 ± 3.6</td>
<td>28.4 ± 3.2</td>
<td>26.3 ± 3.2</td>
</tr>
<tr>
<td>Hgb, g/dl</td>
<td>9.9 ± 1.3</td>
<td>9.9 ± 1.2</td>
<td>9.2 ± 1.1</td>
</tr>
<tr>
<td>Change in plasma volume, %</td>
<td>- +0.46 ± 0.6</td>
<td>- -7.1 ± 9.3*</td>
<td>- +0.26 ± 4.8</td>
</tr>
</tbody>
</table>

*p<0.05 compared with value at PEEP = 0 during the same study period.
†p<0.05 compared with nonseptic value at the same PEEP level.
‡p<0.05 compared with the septic value at the same PEEP level.
or HO, in any of the septic study periods. However, PEEP was associated with an increase in Hct and a depression in calculated plasma volume during the septic 1 study (Table 2).

**PEEP's Effects on Hindlimb Fluid Flux (Table 2)**

Prefemoral Qf rose during all PEEP studies, and the magnitude of this increase was similar in all three study periods. [(L/P)TP] ratios fell only during the baseline and septic 1 studies and the CTP was not altered by PEEP during any of the three studies. An example of the effect of PEEP on the time course of one experiment is shown in Figure 4. The response of changes in Qf was found to plateau quickly, since the mean increase in Qf was similar between the first and last 30 min of the 2-h PEEP experiment in all three study periods (baseline, 2.6 ± 1.4 vs 2.6 ± 1.1; p = NS; septic 1, 2.9 ± 1.5 vs 3.2; P = NS); (septic 2, 2.1 ± 0.9 vs 2.3 ± 0.5 ml/30 min; p = NS). Finally, the calculated Pc rose with PEEP during all study periods, and the (Pc - [πp - πt]) gradient increased only during the baseline and septic 2 PEEP studies.

**DISCUSSION**

While the effects of PEEP on pulmonary gas exchange and the core circulations is well-known, its effect within the peripheral microcirculations has not been as thoroughly evaluated. Szabo and Magyar demonstrated that an increase in interstitial fluid content followed an elevation in the CVP during experimentally induced right heart failure. We hypothesized that PEEP would similarly augment peripheral Qf, since it is likely that Pc ap is increased by PEEP ventilation following an increase in intrathoracic pressures and subsequent decrease in venous return. We also hypothesized that any increase in Qf during PEEP would be magnified in sepsis, since systemic microvascular permeability is increased in this disease and an elevated Pc ap disproportionately increases Qf when permeability of the microvascular fluid-exchanging membrane under evaluation is augmented. We found that PEEP, 15mm Hg, augmented microvascular Qf in tissues drained by the prefemoral lymph node of sheep in both hyperdynamic septic and nonseptic study conditions.

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21603/ on 06/26/2017)
The Model

We evaluated the effects of PEEP on peripheral water and protein flux within the hindlimb of sheep by measuring changes in Qt and CTP, respectively, from the efferent duct of the prefemoral lymph node. To determine the effects of PEEP in sepsis, we modified the small animal model described by Wichterman et al. Similar to the central circulatory profile considered most typical of clinical sepsis, a progressive increase in CI, with unchanged mean systemic perfusing pressures, characterized the septic study periods in this experiment. These changes were also associated with the development of a polymicrobial bacteremia and an increase in both systemic VO₂ and O₂d. Similar to the peripheral manifestations of systemic sepsis, we previously documented an increase in microvascular permeability to water and protein in both the lung and hindlimb of this septic model. Thus, this model fulfills the majority of criteria required to infer that changes herein described would likely characterize early human sepsis.

Although we previously described an increase in prefemoral Qt during hyperdynamic bacterial sepsis in sheep, this was not confirmed in the current experiment. However, changes in hindlimb microvascular permeability were also evaluated both by measuring 125I-HSA flux from blood to lymph and by qualitative morphologic examination. An increase in interstitial fluid, qualitatively staining for albumin with greater intensity than during the nonseptic study, was found in both septic studies (Fig 2). We also found that the (L/P) 125I HSA ratios increased during the septic study. These latter data imply that increased hindlimb microvascular permeability to protein likely characterized the septic studies in these experiments, even though prefemoral Qt was not increased. A number of factors may have prevented an increase in prefemoral Qt as an expression of increased microvascular permeability during the septic studies. Thus, a reduced capillary surface area across which microvascular fluid exchange occurs could have accompanied a decrease in blood flows to skin, subcutaneous tissue and muscle during the septic studies. Further, reduced lymphatic clearance of excessive interstitial fluid content during the septic studies may have prevented an increase in prefemoral Qt since endotoxin has been shown to decrease lymphatic propulsive activity.

Effect of PEEP on Peripheral Water and Protein Flux

An immediate, sustained, and similar increase in peripheral Qt followed the application of PEEP 15 mm Hg, during all three study periods, while the (L/P)TP ratio was simultaneously depressed in only the baseline and septic 1 studies. A 30 percent increase in Qt, with a decrease in [L/P]TP ratios, implies that PEEP augmented the microvascular Qf during the baseline and septic 1 study periods by a hydrostatic effect. Although this interpretation is supported by the simultaneous increase in Pcap, the formula used to calculate Pcap did not account for potential changes in either of the precapillary or postcapillary resistances within the septic microcirculation. Nonetheless, these changes in Qt probably reflected a direct effect of PEEP on the Pcap, as any possible effect of a stress-related increase in circulating catecholamines on the microcirculation was minimized by appropriate sedation and by maintaining high filling pressures, thereby preventing a depression in the CO by PEEP. The effects of PEEP on peripheral Qt and CTP in both baseline and septic 1 study conditions were qualitatively similar to the reported effects of endotoxin on Qf in the soft tissue microcirculations, wherein Demling et al concluded that endotoxin augmented prefemoral Qt by a "hydrostatic" mechanism following an increase in the CVP.

In contrast to baseline and septic 1 studies, the increase in prefemoral Qt during the septic 2 PEEP study was not accompanied by a change in either of the (L/P)TP ratios or the calculated πi. This dissimilarity in response of prefemoral Qt to PEEP during the septic studies requires that several possibilities be considered. First, microvascular surface area may have increased in the septic 2 study to explain an increase in Qt with unaltered (L/P)TP ratios. Insofar as the CI was not augmented by PEEP, and microsphere-derived hindlimb blood flow is not increased during PEEP, this explanation may not be the most plausible. Second, a washout of interstitial protein prior to the septic 2 PEEP study may have established filtration-independent conditions of Qt. Finally, the effects of PEEP during the septic 2 study might have been expressed across a microvascular membrane characterized by increased permeability to protein. Although the data do not allow a conclusive mechanistic statement, it is apparent that PEEP increased the microvascular Qf during the septic 2 study period but had different effects on both the (L/P)TP ratio and the πi than was observed in the other study periods.

Finally, an increase in prefemoral Qt during the septic 1 study was associated with an increase in both hematocrit and total protein. Similar changes which followed an increase in intrathoracic pressures have been interpreted to reflect a concurrent decrease in plasma volumes. Therefore, we conclude that PEEP promoted an increase in the transmicrovascular flux of fluid within the systemic microcirculations by two lines of reasoning: firstly, prefemoral Qt consistently rose with the application of 15 mm Hg PEEP; and, second, hemoconcentration was demonstrated during the septic 1 PEEP study.

Despite our prior reasoning that the septic study
conditions were likely different from baseline study by virtue of an increase in hindlimb microvascular permeability and that an increase in Pcap should, therefore, have disproportionately increased prefemoral \( Q_l \) during the latter study, the (PEEP \times sepsis) interaction was not associated with a greater increase in prefemoral \( Q_l \) than was noted during the baseline study. The interactive effects of PEEP and sepsis either to reduce microvascular surface area and/or to depress interstitial fluid clearance may have prevented a greater increase in \( Q_l \) during the septic vs the baseline studies.

Clinical Considerations

Several clinical consequences could result from a protracted increase in peripheral \( Q_l \) during PEEP-ventilation. First, reduced intravascular volume may complicate PEEP, evident by the hemocoagulation demonstrated during the septic 1 studies. In addition to depressing ventricular preload by impeding venous return, it is possible that a depression in CO during PEEP ventilation may be contributed to by an absolute vs relative decline in intravascular volume.

Second, Harms et al\(^{10} \) demonstrated that an increase in prefemoral \( Q_l \) of 100 percent was associated with a significant increase in tissue water content. The effects of excessive tissue edema to augment infection rates and decrease wound healing have been documented.\(^{33} \) Sepsis imposes an added burden to the host in the regulation of tissue \( O_2d \).\(^{1,5} \) As demonstrated in the septic 2 study, this disease is associated with a depression in peripheral \( O_2E \), perhaps the result of compression of the capillary bed by an accumulation of excessive interstitial edema.\(^{7} \) Therefore, a protracted increase in interstitial fluid volumes during PEEP therapy may further impede adequate tissue \( O_2d \).

Administration of PEEP increased the prefemoral \( Q_l \) in both nonseptic and septic conditions in contrast to the negligible effects of PEEP on pulmonary microvascular fluid exchange.\(^{34,35} \) An increase in hindlimb extravascular water content and a decrease in effective intravascular volume likely resulted. Theoretically, both a depression in CO and an increase in tissue edema during PEEP ventilation might contribute to a reduction in tissue \( O_2d \) in septic patients. We think that the effects of PEEP on the peripheral microcirculation require further evaluation before it can be concluded that the central cardiorespiratory sequelae of PEEP are the only significant factors that influence tissue \( O_2d \) during this form of respiratory support.

\(^{14} \) Source provided by Mrs.

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