The effect on pulmonary fluid balance of adrenergic receptor agonist agents commonly employed in clinical sepsis has not been well characterized. Therefore, we tested the hypothesis that dobutamine would increase pulmonary microvascular fluid flux in experimental sepsis-induced lung injury. To define the effects of this synthetic catecholamine on pulmonary lymph flow (Qₐ), we infused dobutamine in sheep at two doses in sequence (5µg/kg/min and 10µg/kg/min) before and after the induction of intraperitoneal sepsis which resulted in the development of lung microvascular injury. In the nonseptic state, cardiac output increased at both 5µg/kg/min and 10µg/kg/min (22 and 36 percent, respectively), while Qₐ was unchanged from baseline (for 5µg, ΔQₐ = +0.44±1.35 ml/15 min; not significant) (for 10µg, ΔQₐ = −0.20±1.0 ml/15 min; not significant).

Values for the ratio of lymph/plasma total protein levels ([L/P]TP) fell modestly in the nonseptic study at both doses (p<0.05). With established sepsis syndrome, Qₐ increased from the nonseptic baseline study (2.99±1.8 to 7.01±3.95 ml/15 min; p<0.05), without change in [L/P]TP ratios or the calculated microvascular hydrostatic pressure (Pmv). During sepsis, dobutamine infusion was again associated with an increase in cardiac output at both the 5µg/kg/min (+29 percent) and 10µg/kg/min (+33 percent) doses, while Qₐ increased modestly only with the lower dose of dobutamine infused (5µg/kg/min, ΔQₐ =1.80±2.2 ml/15 min; p<0.05). In this model of sepsis-induced lung injury, dobutamine increased systemic flow without substantially augmenting Qₐ.

The development of noncardiac pulmonary edema (NCPE) is the consequence of an increase in permeability of the lung's microvascular exchanging membrane. The result is in an abnormal accumulation of extravascular lung water (EVLW) at normal microvascular hydrostatic pressures (Pmv). Experimental findings have also documented that an increase in either the Pmv or the surface area of the lung's microvascular exchanging membrane secondarily promotes accumulation of extravascular lung water in noncardiac pulmonary edema.

Patients with the adult respiratory distress syndrome (ARDS) frequently require pharmacologic support to maintain adequate peripheral oxygen availability. Beta-adrenergic receptor agonists may thereby be employed to augment cardiac output (hence systemic oxygen transport), even when systemic pressures are considered to be within normal ranges; however, theoretically, such agents might depress systemic oxygen transport if, among other reasons, a reduction in arterial oxygen saturation resulted from enhanced edema formation or a loss of hypoxic vasoconstriction. In ARDS, β-adrenergic receptor agonists might worsen pulmonary microvascular fluid flux, thereby further augmenting edema formation and depressing arterial oxygen content, by increasing the surface area across which fluid exchange occurs within the lung, by primarily altering the lung's endothelial permeability characteristics, or by effecting an increase in the Pmv.

In healthy animals, Minnear et al7 demonstrated that an infusion of norepinephrine was associated with an increase in pulmonary lymph flow (Qₐ) and a concurrent decrease in the ratio of lymph-to-plasma total protein levels ([L/P]TP); these data implied that an increase in pulmonary microvascular fluid flux during infusion of norepinephrine was due to an increase in the Pmv. Subsequently, Minnear and Malik8 proposed that sympathetic stimulation might directly augment lung microvascular permeability to protein. Conversely, Walman et al9 reported that pre-treatment with isoproterenol ameliorated an increase in the permeability of the lung's microvasculature.
secondary to an infusion of endotoxin. Uncertainty therefore remains as to the effects of exogenously administered catecholamines on microvascular fluid flux in healthy animals; there may be even less appreciation of the effect of such agents on pulmonary microvascular fluid flux when administered during a period of established lung injury. Dobutamine is a synthetic β-adrenergic receptor agonist which is frequently used in clinical sepsis, the latter an important cause of noncardiac pulmonary edema. Since it has been suggested that dobutamine may be a preferred adrenergic receptor agonist to augment systemic flows in acute hypoxic respiratory failure, we examined its effects on pulmonary microvascular fluid flux in sheep in a model of intraabdominal sepsis which is complicated by lung injury.

**MATERIALS AND METHODS**

**Experimental Preparation**

Ten mature Suffolk sheep, weighing 30 to 40 kg (0.9 to 1.2 m² of body surface area), were prepared with chronic lymph fistulae using a modification of the technique described by Staub et al. Before study the sheep were premedicated with atropine sulfate and were then anesthetized and intubated. We cannulated the aorta with a nonheparinized Silastic catheter (medical grade tubing; 0.125 outer diameter, Dow Corning) and the pulmonary artery with a No. 8 French, right-heart flow-directed thermocatheter (Edwards model 93A-131). The right-heart catheter position was confirmed by the presence of typical pressure recordings. With the balloon inflated, a pulmonary arterial wedge tracing was documented. The balloon was then deflated, and the catheter was flushed for the duration of the experiment with a continuous infusion of 5 percent dextrose in water, to which 1,000 units of heparin had been added (1.0 ml/hr).

Using a right posterolateral thoracotomy through the sixth intercostal space, the efferent duct of the caudal mediastinal lymph node was then cannulated with a nonheparinized Silastic catheter (medical grade tubing with 0.025 inner diameter and 0.047 outer diameter, Dow Corning). The catheter was secured and externalized through the chest wall. The tail of the caudal mediastinal lymph node was identified, ligated, and divided below the level of the inferior pulmonary ligament. To further reduce potential for contamination by nonpulmonary lymph, all identifiable diaphragmatic and chest wall afferent lymphatic vessels were cauterized in a manner similar to that described by others. Following a left thoracotomy through the fourth intercostal space, the left atrium was then catheterized with a No. 16 French Foley catheter.

This protocol was approved by the University of Western Ontario’s committee governing the experimental care of animals. To ensure that the animals did not suffer discomfort when studied while awake, we administered 50 mg of meperidine intravenously every six to eight hours; in the immediate postoperative period, this was supplemented with acetylpromazine (25 mg) intravenously to minimize the pain of the thoracotomies and a subsequent laparotomy.

**Experimental Protocol**

Baseline studies were performed over a 120-minute period approximately three to four days after recovery from preliminary surgery. Pulmonary lymph was collected and measured for volume every 15 minutes; lymph was pooled at the end of the two-hour baseline period for measurement of total protein and albumin. At the midpoint of this baseline "nonseptic" study, we measured systemic and pulmonary arterial pressures, as well as cardiac output. Blood was drawn from the arterial line and distal port of the right-heart catheter for chemical analysis, hematologic studies, and measurement of arterial and central venous blood gas levels. Dobutamine (500 mg dissolved in 500 ml of 5 percent dextrose in water) was then sequentially administered at two doses (5 μg/kg/min and 10 μg/kg/min) for a 60-minute infusion period with each. The first 15 to 30 minutes of infusion at each dose represented a period of equilibration. Pulmonary lymph was collected and measured for volume during each of the last two 15-minute periods of infusion; it was subsequently pooled for measurement of total protein and albumin.

Blood was drawn for hematologic studies, chemical analysis, and blood gas levels at the end of each of the last two 15-minute periods of infusion. We also repeated measurement of the cardiac output, and systemic and pulmonary arterial pressures at the same time. Therefore, values reported during infusion of the drug at both doses represent the average of two measurements obtained during two timed 15-minute periods of collection.

Following the nonseptic study, an intra-abdominal source of sepsis was created in the sheep, as previously described. Under general anesthesia with halothane, a lower midline laparotomy was performed; the cecum and ileocecal valve were then identified, and approximately 6 to 8 cm of the distal cecum was devascularized. The bulk of fecal material was milked back into the proximal cecum and right colon. The distal cecum was circumferentially ligated with a No. 2 silk tie below the level of the ileocecal valve. After making a 2-cm perforation in the cecal tip, the compromised bowel was returned to the right lower quadrant. The gastrocolic omentum was then ligated and divided to prevent any early localization of the subsequent inflammatory process. The abdomen was closed in layers, and all animals were returned to their cages and allowed free access to food and water.

"Sepsis syndrome," complicated by pulmonary microvascular injury, was defined as an increase in cardiac output and Qo, the latter to levels at least 30 percent above preseptic measurements, this usually occurred between 24 and 48 hours after establishing intraabdominal contamination. At this time, baseline septic measurements were performed, as previously described for the nonseptic study. Dobutamine was then infused for 60 minutes at each of the two doses defined; all measurements previously detailed were repeated and averaged during the last two 15-minute periods of infusion at both the 5 μg/kg/min and 10 μg/kg/min doses.

**Specific Measurements**

We collected pulmonary lymph in graduated heparinized tubes. From pooled lymph specimens, we measured total protein and albumin concentrations (in grams per deciliter) by the Biuret method using an automated system (Auto Analyzer, Technicon Instruments); duplicate samples differed by less than 5 percent.

At the time of lymph collection, we also measured total protein and albumin concentration (in grams per deciliter). With appropriate temperature correction, we measured oxygen tension (P0₂, in millimeters of mercury) (AME-1 blood gas analyzer) and oxygen saturation (SO₂, in percent) (Hemoximeter, Radiometer) of both arterial (eg, PaO₂) and mixed venous (eg, PV0₂) blood drawn from the carotid arterial line and the distal lumen of the right-heart catheter, respectively. Blood for determining gas levels was drawn into heparinized syringes and maintained in ice until determination was performed within 15 minutes of collection.

We measured systolic, diastolic, and mean values for systemic blood pressure and for pulmonary arterial pressure and measured left atrial (LAP) and pulmonary arterial wedge pressures (PCWP) with an arterial/venous pressure transducer (Hewlett-Packard) and a digital display with a continuous paper recording system (Hewlett-Packard arterial/venous pressure module 7820B). Transducers were leveled to the humeral tuberosity, taken as the level of the right atrium in sheep. The cardiac output (in liters per minute) (CO) was determined in triplicate by a thermodilution technique with a
Table 1—Infusion of Dobutamine in Ten Nonseptic Sheep

<table>
<thead>
<tr>
<th>Data*</th>
<th>Baseline</th>
<th>5μg/kg/min</th>
<th>10μg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP, mm Hg</td>
<td>95 ± 7</td>
<td>98 ± 6</td>
<td>89 ± 7†§</td>
</tr>
<tr>
<td>HR, beats per min</td>
<td>113 ± 24</td>
<td>148 ± 30</td>
<td>192 ± 31</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>19.3 ± 4.9</td>
<td>19.4 ± 4.3</td>
<td>19.5 ± 3.9</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>5.8 ± 4.2</td>
<td>6.6 ± 3.6</td>
<td>7.2 ± 4.5</td>
</tr>
<tr>
<td>LAP, mm Hg</td>
<td>2.1 ± 2.9</td>
<td>2.0 ± 3.3</td>
<td>2.0 ± 3.6</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.96 ± 1.4</td>
<td>7.18 ± 1.6</td>
<td>7.99 ± 1.8§</td>
</tr>
<tr>
<td>SVI, m³/min/m²</td>
<td>50 ± 16</td>
<td>46 ± 12</td>
<td>37 ± 9†</td>
</tr>
<tr>
<td>PVRI, dynes/cm²·m⁻⁵/m²</td>
<td>201 ± 41</td>
<td>161 ± 30†</td>
<td>137 ± 29‡</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>97.6 ± 20.3</td>
<td>94.7 ± 12.8</td>
<td>91.1 ± 13.4</td>
</tr>
<tr>
<td>PVO₂, mm Hg</td>
<td>42.3 ± 5.2</td>
<td>49.4 ± 5.1</td>
<td>51.7 ± 5.9§</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>37.2 ± 5.6</td>
<td>36.0 ± 3.4</td>
<td>37.2 ± 4.2</td>
</tr>
<tr>
<td>VO₂, m³/min/m²</td>
<td>196 ± 78</td>
<td>145 ± 30</td>
<td>148 ± 36</td>
</tr>
<tr>
<td>O₂t, ml/min/m²</td>
<td>705 ± 215</td>
<td>950 ± 272+t</td>
<td>1,009 ± 247§</td>
</tr>
<tr>
<td>Pmv, mm Hg</td>
<td>11.2 ± 4.1</td>
<td>11.6 ± 3.6</td>
<td>12.3 ± 4.2</td>
</tr>
<tr>
<td>µPmv, mm Hg</td>
<td>17.9 ± 3.1</td>
<td>17.8 ± 2.9</td>
<td>17.4 ± 2.4</td>
</tr>
<tr>
<td>µPmv-µPmv, mm Hg</td>
<td>10.6 ± 2.4</td>
<td>9.8 ± 2.7§</td>
<td>9.8 ± 2.77</td>
</tr>
<tr>
<td>Q₁, ml/15 min</td>
<td>7.4 ± 1.9</td>
<td>7.8 ± 1.4</td>
<td>7.3 ± 1.9</td>
</tr>
<tr>
<td>[L/P]TP, [L/P]albumin</td>
<td>2.99 ± 1.8</td>
<td>3.41 ± 2.1</td>
<td>3.20 ± 1.9</td>
</tr>
<tr>
<td>[L/P]TP, [L/P]TP</td>
<td>0.68 ± 0.08</td>
<td>0.64 ± 0.07</td>
<td>0.64 ± 0.09</td>
</tr>
<tr>
<td>C₈,</td>
<td>1.99 ± 1.09</td>
<td>2.34 ± 1.61</td>
<td>2.09 ± 1.37</td>
</tr>
</tbody>
</table>

*BP, Blood pressure; HR, heart rate; PAE, pulmonary arterial pressure; PCWP, pulmonary arterial wedge pressure; LAP, left atrial pressure; CO, cardiac output; and O₂t, systemic oxygen transport.
†Each drug interval reflects data collected in last 30 minutes of 60-minute drug infusion.
‡p<0.05 compared to baseline (Student’s paired t-test).
§p<0.05 compared to 5μg/kg/min (Student’s paired t-test).

We calculated the colloid osmotic pressure in both serum (µPmv) and lymph (µPmv) and corrected for the albumin/globulin ratio.6 The pulmonary vascular resistance index (PVRI), stroke volume index (SVI), systemic oxygen consumption (VO₂), and oxygen transport, (O₂) indexed for body surface area (BSA), were calculated from measured hemodynamic parameters. Body surface area for sheep was calculated by the following formula: BSA = (weight in kg × 0.75) / (70/BSA).7 We calculated the mean hydrostatic pressure within the pulmonary microcirculation (Pmv) as follows:8 Pmv = LAP + 0.4 (mean PAP – LAP), where LAP is left atrial pressure and PAP is mean pulmonary arterial pressure. From lymph flow (Q₈, in milliliters per 15 minutes) and [L/P]TP, we also calculated the clearance of lymph protein (C₈) as: Q₈ × [L/P]TP (in milliliters per 15 minutes).

Statistics
Data are expressed as the mean ± standard deviation. Statistical comparisons were made using Student’s paired or unpaired t-test, as indicated, and a p value of less than 0.05 was considered significant. Regression analyses were also used with independent variables to describe and predict a dependent variable as a function of these variables.

Observations

Nonseptic Study
The infusion of dobutamine was associated with a modest fall in the mean blood pressure at the 10μg/kg/min dose but was without effect on the mean pulmonary arterial pressure at either dose (Table 1 and Fig 1). The cardiac output increased progressively with both doses, while the measured pulmonary arterial wedge pressure, left atrial pressure, and calculated Pmv remained unchanged. Systemic oxygen transport increased at both doses, and the PV0₂ increased concurrently.

Dobutamine did not significantly affect Q₁ or the [L/P]TP at either dose. The calculated mean µPmv fell with both doses (p<0.05), although the µPmv-µPmv gradient was unchanged from baseline. Therefore, the C₈ remained unchanged from baseline during the infusion of dobutamine of either dose.

We found no significant relationship between changes in Q₁ and cardiac output (CO) at either dose (5μg/kg/min, ΔQ₁ = 1.3 – 0.66 ΔCO; r = –0.12) (10μg/kg/min, ΔQ₁ = 1.70 – 0.311 ΔCO; r = –0.36),
Table 2—Infusion of Dobutamine in Septic Sheep

<table>
<thead>
<tr>
<th>Data*</th>
<th>Baseline</th>
<th>5 μg/kg/min</th>
<th>10 μg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BP, mm Hg</td>
<td>102 ± 10;</td>
<td>92 ± 17§</td>
<td>79 ± 13§</td>
</tr>
<tr>
<td>HR, beats per min</td>
<td>134 ± 39;</td>
<td>182 ± 58.1;</td>
<td>205 ± 49§</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>27.6 ± 13.3;</td>
<td>28.1 ± 12.5</td>
<td>27.3 ± 13.1</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>9.5 ± 7.8;</td>
<td>11.6 ± 8.9§</td>
<td>12.1 ± 10.4</td>
</tr>
<tr>
<td>LAP, mm Hg</td>
<td>3.2 ± 6.9;</td>
<td>3.5 ± 8.0</td>
<td>4.4 ± 9.7</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>6.99 ± 1.9;</td>
<td>8.7 ± 1.8§</td>
<td>9.19 ± 2.5§</td>
</tr>
<tr>
<td>SVI, ml/min/m²</td>
<td>53 ± 18;</td>
<td>49 ± 19</td>
<td>44 ± 15</td>
</tr>
<tr>
<td>PVRI, dynes-sec/cm²</td>
<td>235 ± 124;</td>
<td>182 ± 94§</td>
<td>58 ± 71§</td>
</tr>
</tbody>
</table>

PaO₂, mm Hg | 87.5 ± 12.7; 88.1 ± 14.6 | 83.3 ± 15.5 |

PvO₂, mm Hg | 45.3 ± 4.4; 48.1 ± 5.8 | 48.5 ± 4.6 |

PaCO₂, mm Hg | 43.3 ± 6.3; 40.3 ± 7.6§ | 42.5 ± 6.4 |

V₀₂, ml/min/m² | 156 ± 52; 163 ± 39 | 156 ± 56 |

O₂t, ml/min/m² | 720 ± 197; 930 ± 271§ | 907 ± 245§ |

Pmv, mm Hg | 17.7 ± 9.7; 17.3 ± 10.2 | 18.0 ± 11.5 |

πmv, mm Hg | 13.8 ± 2.8; 13.2 ± 2.3 | 12.2 ± 2.2 |

πmv, mm Hg | 7.1 ± 3.3; 6.2 ± 3.0§ | 6.1 ± 2.9 |

πmv-πpmv, mm Hg | 6.7 ± 2.8; 7.1 ± 2.4 | 6.1 ± 1.7 |

Q̇L, 15 min | 7.0 ± 3.9; 8.7 ± 4.8§ | 7.8 ± 5.8 |

[L/P]TPF | 0.57 ± 0.2; 0.52 ± 0.2§ | 0.53 ± 0.2 |

[L/P]albumin | 0.59 ± 0.22; 0.57 ± 0.21 | 0.61 ± 0.17 |

C₀L | 3.58 ± 1.52; 4.28 ± 2.14§ | 4.00 ± 2.46 |

*BP: Blood pressure; HR: heart rate; PAP: pulmonary arterial pressure; PCWP: pulmonary arterial wedge pressure; LAP: left atrial pressure; CO: cardiac output; and O₂t, systemic oxygen transport.

†Each drug interval is last 30 minutes of 60-minute drug infusion.

§p<0.05 compared to baseline nonseptic study.

Table 2—Infusion of Dobutamine in Septic Sheep

Unlike data reported by Coates et al, where with exercise an increase in Q̇L was significantly related to an increase in the cardiac output.

**Septic Study**

With definition of the “sepsis syndrome,” all sheep demonstrated a higher mean systemic blood pressure, mean pulmonary arterial pressure, heart rate, and PaCO₂ (Table 1 and 2; Fig 1). Similarly, when compared to the baseline nonseptic study, Q̇L had increased, while the values for [L/P]TPF ratios were unchanged; C₀L, therefore, was also increased above baseline nonseptic study. Both the πmv and πpmv gradient remained unchanged (Table 2). Again, we found no correlation between the cardiac output and Q̇L at baseline, when combining both septic and nonseptic studies (r = 0.22; p not significant). We have previously interpreted the finding of an increase in Q̇L, without a significant fall in [L/P]TPF ratios, as indicative of a permeability lesion within the pulmonary microvascular surface of sheep with an intraperitoneal focus of sepsis.

During the septic study, the infusion of dobutamine was associated with a progressive decline in the mean systemic blood pressure throughout the two dosing regimens employed (Table 2); however, it was without effect on the mean pulmonary arterial pressure. Since the cardiac output increased with both doses, the calculated PVRI, therefore, fell. Systemic oxygen transport increased at both doses, although the PaO₂ and systemic V̇O₂ remained unchanged. The calculated Pmv did not change, while the pulmonary arterial wedge pressure increased significantly above baseline at only the 5 μg/kg/min dose (+22 percent) and the left atrial pressure remained unchanged from baseline at both doses.

A significant increase in Q̇L was noted with low-dose infusion (+24 percent) but not at the higher dose; [L/P]TPF ratios also fell at the low dose but not at the higher dose. Therefore, C₀L increased significantly from the baseline septic study only with the 5 μg/kg/min dose and not with the 10 μg/kg/min dose. Except for the highest dose employed (10 μg/kg/min, y = 0.37 + 0.91x; r = 0.67), no significant relationship was found between changes in Q̇L and changes in the cardiac output (CO) (5 μg/kg/min, ΔQ̇L = 1.31 + 0.13 CO; r = 0.014).

**DISCUSSION**

The flow-dependency of systemic V̇O₂, which is frequently demonstrable when ARDS complicates the “sepsis syndrome,” may clinically dictate the use of β-adrenergic receptor agonists when cardiac output (hence systemic oxygen transport) is not deemed sufficient to satisfy peripheral oxygen needs. Theoretically, the administration of β-adrenergic receptor agonists could increase pulmonary microvascular fluid flux in ARDS and thereby lead to further edema; however, we found in this study that dobutamine did not substantially increase Q̇L in an animal model of sepsis-induced microvascular pulmonary injury when infused at a dose of 10 μg/kg/min, although a modest increase (+24 percent) was demonstrable when dobutamine was infused at a lower dose.

To augment central flows and systemic oxygen transport in ARDS, the use of β-adrenergic receptor agonists may represent a presumed advantage when compared to intravascular volume loading. An increase in the Pmv, which might well accompany an increase in ventricular preload following volume loading, should augment Q̇L and extravascular lung water accumulation to a greater degree in ARDS than when the normal permeability characteristics of the lung’s microvascular membrane remain unaffected by underlying disease. Nevertheless, it could be argued that the administration of β-adrenergic receptor agonists might increase extravascular lung water accumulation in ARDS by independently affecting any of the major determinants of pulmonary microvascular fluid flux which are defined within the Starling equation, specifically the following: pulmonary microvascular permeability; the Pmv; and the perfused surface area of
the lung's exchanging microvasculature. Studies from which the effects of β-adrenergic receptor agonists on lung microvascular fluid flux might be related to the clinical correlate have either been performed in healthy animals or were designed as a pretreatment protocol; conclusions therein derived may well not characterize the effects of exogenous catecholamines on both lung microvascular fluid flux and systemic hemodynamics in the "sepsis syndrome" is also critically important; for example, endotoxin models of on both lung microvascular fluid flux and systemic hemodynamics in the "sepsis syndrome" is also critically important; for example, endotoxin models of lung microvascular injury may only reflect a later period in a progression of the "sepsis syndrome" because of the marked dissimilarities noted in both flow and pressure characteristics (among others) between this model and early human sepsis. Therefore, when administered to an endotoxic model, conclusions about the effects of β-adrenergic receptor agonists on lung fluid balance may also not represent their real effects during the early phases of ARDS complicating human sepsis.

Since dobutamine has been recommended as an adrenergic receptor agonist which might be used in preference to dopamine when systemic flows require pharmacologic support in ARDS, we studied its effects on fluid flux in an animal model of peritonitis which is characterized by lung microvascular injury. This model seems more representative of early clinical sepsis than are endotoxic models, since it is characterized by a high systemic flow and low peripheral resistance state, with maintenance of systemic pressures. We evaluated the effects of dobutamine on microvascular fluid exchange in the lung of chronically cannulated sheep by using changes in the magnitude of Q̇ to reflect changes in water flux and using changes in the C̃ to represent changes in protein flux.

The remote effects of surgically induced peritonitis on the lung's microvascular exchanging membrane were seen as an increase in Q̇, without a significant depression in [L/P]TP ratios. Hence, C̃TP or protein flux, was also increased with the onset of "sepsis syndrome." Concurrently, both the cardiac output and the mean pulmonary artery pressure were greater than was observed in the nonseptic studies. An increase in Q̇, with unchanged [L/P]TP ratios, must represent the effects of an increase in either endothelial permeability or in the surface area of the lung's exchanging membrane on lung microvascular fluid flux. Although an increase in Q̇ secondary to intraperitoneal contamination may arguably have been the consequence of an increase in the lung's perfused surface area, previous morphologic examination of this model has documented that a permeability lesion is the primary explanation for an observed increase in Q̇ with the onset of sepsis. The lack of any demonstrable correlation between changes in Q̇, and cardiac output during the septic studies would lend further support to our contention that an increase in Q̇, with unchanged [L/P]TP ratios was not primarily the consequence of an alteration in the lung's perfused surface area. Therefore, bacterial peritonitis in this animal model was associated with an increase in C̃TP secondary to an increase in pulmonary microvascular permeability. Undoubtedly, an increase in microvascular surface area or the Pmv (or both) may also contribute to the augmented Q̇, documented, as has been demonstrated in endotoxic models of lung injury.

Dobutamine had no net effect on pulmonary fluid flux in the nonseptic studies. In contrast, its effects in the septic state were inconsistent. At a dose of 5µg/kg/min, a modest (24 percent) increase in Q̇ was demonstrable when compared to baseline, while no significant change was evident with the 10µg/kg/min dose; with an increase in Q̇, [L/P]TP ratios fell. Reasons for an increase in Q̇, at the lower infused dose might include an effect of dobutamine to increase either the Pmv or the surface area of the lung's microvasculature across which fluid exchange occurs. Since we found no relationship between changes in cardiac output and Q̇, we would conclude that changes in surface area were not likely to be responsible for the slight increase noted in Q̇. Therefore, the data are most consistent with an interpretation that a "hydrostatic" effect was primarily responsible for the changes documented in pulmonary Q̇, with low-dose dobutamine infusion. Since the pulmonary arterial wedge pressure was significantly elevated from baseline at this dose, without any concurrent change in the left atrial pressure, it is conceivable that a pressure gradient was established between the left atrium and the lung's microvascular exchanging membrane, and that such was thereby responsible for the modest increase in Q̇ observed during low-dose dobutamine infusion.

Why we found no effect of dobutamine on Q̇, at the 10µg/kg/min dose, nor on Q̇ at either dose in the nonseptic study, is speculative. As suggested by O'Bradovich and Coates, β-adrenergic receptor agonists might well not increase the surface area of the lung's exchanging membrane, as would be expected from a comparable increase in cardiac output when mediated by exercise; however, in the septic study, such may not be a sufficient explanation, as changes in those factors responsible for pulmonary microvascular fluid flux should effect an exaggerated response in Q̇, when the microvascular membrane is characterized by a permeability lesion. Thus, an increase in Q̇, of only 24 percent during low-dose dobutamine infusion in the septic study is in contrast to an increase in Q̇, of 296 percent when cardiac output was increased by 85 percent in exercising sheep where microemboli were
used to concurrently induce a permeability defect. Therefore, it may be suggested that QL should have increased more than was observed with either dose of dobutamine infused during the septic study. It is possible that dobutamine minimized an anticipated increase in QL in both the preseptic and septic studies by primarily affecting those mechanisms which govern the transendothelial flux of fluid and protein at the level of the pulmonary microvascular membrane. A similar explanation was proposed by Walman et al when pretreatment with the β-adrenergic agonist, isoproterenol, reduced edema formation following an infusion of endotoxin. To further support our suggestion that dobutamine may have functionally reduced the effects of altered endothelial permeability characteristics on microvascular fluid flux in this study, Hakim et al concluded that β-adrenergic receptors regulated pulmonary transendothelial transport of fluid and proteins since β-adrenergic blockade with propranolol was associated with an increase in QL. Also, in the peripheral microvasculature, β-adrenergic receptor agonists demonstrably inhibit edema formation and transmicrovascular protein flux, an observation that cannot be explained by their effects on microvascular pressure, blood flow, or surface area. The rationale underlying such a protective action of β-adrenergic receptor agonists within the pulmonary microvasculature is purely speculative but may reflect the effects of enhanced cyclic AMP generation within the endothelium, perhaps thereby leading to relaxation of mediator-contracted endothelial cells.

Alternatively, dobutamine may have reduced an anticipated increase in QL by affecting the intrinsic propulsive activity of the pulmonary lymphatic vessels; however, it is likely that were dobutamine to have influenced lymphatic contractility, we should have observed an increase in QL, since lymphatic propulsive activity is most likely enhanced by such agents.

Mention should be made of the timing of dobutamine infusion for evaluation of its effects on pulmonary microvascular fluid flux. Parenteral administration of dobutamine is accompanied by a half-life of less than three minutes, and maximum cardiovascular changes reportedly occur at an infused dose of 10 μg/kg/min. Therefore, the period of administration at each dose level in this study (viz., one hour) should have adequately characterized the drug's effects on pulmonary microvascular fluid flux in this model of sepsis, if any, as Coates et al noted that acute changes in QL during exercise in goats were evident within 15 minutes, an effect which had dissipated within 30 minutes following cessation of that protocol.

Regardless of mechanism, dobutamine did not substantially worsen pulmonary microvascular fluid flux, assessed by changes in pulmonary QL, in an animal model of ARDS secondary to the remote effects of intraperitoneal sepsis, except as it may have slightly modified the hydrostatic pressure acting at the level of a damaged pulmonary microvascular bed. In fact, there is reason to speculate that dobutamine protected against what might have been anticipated as a substantial increase in pulmonary QL during the septic studies. Similar conclusions cannot necessarily be extended to the use of other β-adrenergic receptor agonists in ARDS, due to their sometimes unique effect on both the pulmonary microvascular surface area and the Pmv; however, unlike clinical reports, dobutamine administration was not associated with a decline in the left atrial pressure. Nonetheless, its minimal effects on pulmonary fluid balance, as systemic oxygen transport was augmented, support previous suggestions that this β-adrenergic receptor agonist may be an ideal choice in acute hypoxemic respiratory failure secondary to ARDS when systemic flows and systemic oxygen transport need to be pharmacologically supported.

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