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COMBINED MONITORING OF THORACIC DUCT AND LUNG LYMPH DURING *E. COLI* SEPSIS IN AWAKE SHEEP

L. Smith, S. Andreasson, T. Saldéen, B. Risberg

Department of Surgery I, Göteborg University, Göteborg, and Department of Forensic Medicine, University of Uppsala, Sweden

ABSTRACT

A thoracic duct lymph fistula in combination with a lung lymph fistula in the awake sheep was used to evaluate effects of thoracic lymph diversion during a septic insult and to monitor systemic and local changes in the lung and gastrointestinal tract. Live Escherichia coli $10^9 kg^{-1}$ b.w. were infused in 9 sheep. After sepsis, arterial pressure, cardiac output, partial pressure of oxygen, leukocytes and platelets decreased significantly compared to baseline values. Pulmonary arterial pressure increased significantly throughout the experiment with peak values at 44±4 mmHg after 15 minutes. Lung lymph flow (Q_L) (n=6) increased from 2.3±0.5 to 11.2±2.4 ml/30 minutes after 60 minutes. Q_L then decreased but remained elevated. Lymph to plasma protein concentration ratio (L/P) in lung lymph decreased from 0.62±0.02 during baseline to 0.47±0.04 after 60 minutes. L/P then increased and was, after 150 minutes, no longer different from baseline. These lung lymph data favor increased pulmonary microvascular permeability during sepsis. Lymph flow in the thoracic duct (Q_T) (n=9) increased from 34.2±6 to 58.3±9 ml/30 minutes during the first 30 minutes after bacterial infusion. Q_T was, after 90 minutes, back to baseline but then progressively increased. L/P in thoracic lymph steadily increased from 0.56±0.03 to 0.78±0.04. Thromboxane B_2 and 6-keto $PGF_{1\alpha}$ in thoracic duct and lung lymph increased significantly after bacterial infusion and remained elevated thereafter. Combined monitoring of thoracic duct and lung lymph enabled comparison of systemic and pulmonary reactions in septic sheep.

The sheep model, as described by Staub et al (1) with either an acute or a chronic lung lymph fistula, has been extensively used to study effects on respiration and lung circulation after sepsis (2-4). Lung lymph that is continuously collected reflects the pulmonary interstitial fluid and is thus suitable for evaluation of microvascular exchange. For studies of abdominal pathophysiology thoracic duct lymph has similarly been examined (6,7).

After sepsis, increased microvascular permeability and local pulmonary activation of the eicosanoids and various proteolytic systems have been found (4,5). During experimental sepsis pulmonary and gastrointestinal effects have usually been studied separately, but no comprehensive study comparing pulmonary and gastrointestinal effects has been reported (2,8-12). Accordingly, we compared the pulmonary and thoracic duct lymph responses before and after a major septic insult.

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MATERIALS AND METHODS

Preparative procedure

Nine sheep of both sexes with an average weight of 26 kg (range 17-41kg) were used. The sheep were anesthesized with ketamine (500mg i.m.) and thiopentale sodium (20mg/kg b.w. i.v.), intubated and ventilated with air using an Engström respirator. Anesthesia was maintained during surgery by continuous infusion of ketamine. Following the lymph fistula preparations, the sheep recuperated for 3-4 days before experimentation.

On the day of experimentation, the sheep were lightly reanesthetized for 10-15 minutes by ketamine i.v. and catheters for blood sampling and pressure readings were placed in the internal jugular vein and carotid artery. A thermistor tipped, double lumen, flow directed catheter was placed into the pulmonary artery and a 5-Fr catheter with an attached thermistor was placed in the aorta for measurement of cardiac output (Q_t) (Edwards, Lungwater Computer 9130, Santa Ana, California). When the sheep were fully awake they were placed in a cage with free access to water. Volume replacement for loss of lymph and blood was done with lactated Ringer's solution (200ml/hour).

Operative procedure

Lung lymph was collected using the technique described by Staub and coworkers (7). Through a right-sided thoracotomy in the 9th intercostal space, the caudal mediastinal lymph node was divided below the inferior pulmonary ligament. All visible contributory lymphatics were resected. Through another thoracotomy in the 5th intercostal space, the efferent duct from the lung lymph node was cannulated using a heparin glutaraldehyde-treated silastic catheter (OD 1.19mm). The catheter was exteriorized through the 6th intercostal space close to the vertebra. All catheters were of the same length.

Through the right-sided thoracotomies in the 9th and 5th intercostal space the thoracic duct was cannulated caudally, 2-3cm above the diaphragm and proximally just above the inflow of the lung lymph vessel into the thoracic duct using a silastic catheter. The part of the catheter that by-passed the middle portion of the thoracic duct in the thoracic cavity was exteriorized between the 9th and 5th intercostal space and placed subcutaneously.

On the day of experimentation 6 out of 9 lung lymph catheters had a steady flow of clear lymph. Through a small cutaneous cut-down the thoracic by-pass was taken out and divided. All 9 functioned with flow of thoracic lymph and by testing with saline injection the cranial portion was patent in all indicating a functioning by-pass.

Bacterial preparation

An *Escherichia coli* bacteria strain (*E. coli* 06, K13, H1 WHO designation SU 4344/41) from WHO collaborative center for reference and research on Escherichia (State Serum Institute, Copenhagen, Denmark) was used. Ordinary nutrition broth was used for cultivation. The bacteria were washed once prior to infusion and resuspended in 0.9% NaCl to a concentration of $10^9 ml^{-1}$. In all experiments *E. coli* $10^9 ml^{-1}$ b.w. were infused during 20 minutes i.v. The bacterial concentration and strain was confirmed by cultivating, typing and counting bacteria from the infusate. This was only done occasionally as this strain has been used in experimental research for several years with low variability in total number of bacteria and with no contamination.

Measurement

Mean aortic pressure (P_{sa}) was measured in all sheep. Mean pulmonary arterial pressure (P_{pa}) was measured only in 8 sheep for technical reasons. The reference level for pressures was the apex of the shoulder. Cardiac output (Q_t) was

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measured using thermal indicator dilution technique. Thoracic duct and lung lymph were continuously collected and lymph flow was measured at 15 minute intervals. Samples for total protein concentration in plasma and lymph were taken at 30 minute intervals. Thromboxane B_2 (Tx B_2) and 6-keto PG $F_{1\alpha}$ (6-keto) were measured in both lung and thoracic duct lymph in all nine sheep before and at 30, 60, and 180 minutes after bacterial infusion. Hematocrit (Hct), leukocyte and platelet counts were analyzed using standard methods. Partial pressure of oxygen, (P_aO_2), and carbon dioxide (P_aCO_2) in arterial blood were measured using an automated blood gas analyzer.

Experimental procedure

After a baseline period of 60 minutes the sheep received an intravenous infusion of live *E. coli* $1x10^9$ b.w. during 20 minutes. They were then followed for 4 hours.

Biochemical analysis

The total protein concentrations in lymph and plasma were analyzed using Biuret assay on a Grainer autoanalyzer and the lymph to plasma concentration ratio (L/P) was calculated.

Tx B_2 and 6-keto, the stable metabolites of thromboxane A_2 and prostacyclin, were determined by radioimmunoassays (RIA) using radiolabeled antigen and antirabbit antiserum as antibody (6-keto-Prostaglandin $F_{1\alpha}$ ^{125}I RIA Kit and Thromboxane B_2 ^{125}I RIA Kit, New England Nuclear). The Tx B_2 antibody crossreacts 3.9% with PGD_2, 0.2% with PGE_2, 0.1% with PGF_2, 0.06% with 6-keto and PGE_1. The 6-keto antibody crossreacts 2.6% with PGF_2, 1.9% with PGE_1, 1.4% with Tx B_2, 1.1% PGE_2, 0.8% with PGF_1, 0.2% with PGA_2 and PGD_2, 0.05% with arachadonic acid and 0.04% with PGA_2. Each sample was assayed in duplicate (13).

Statistics

Data were expressed as $\bar{X}$±SEM. Significance calculations were made using Wilcoxon Rank test and $p<0.05$ was considered statistically significant.

RESULTS

Hemodynamic and respiratory parameters

During the baseline period before infusion of bacteria, P_{sa} and P_{pa} were stable at 88±9 and 15±0.9mmHg respectively. After infusion of bacteria P_{sa} significantly decreased during 60 minutes to 71±8mmHg but thereafter stabilized. P_{pa} increased significantly during bacterial infusion and peaked at 44±4mmHg after 15 minutes. P_{pa} then decreased and was 22±2.5mmHg after 60 minutes but was still increased over baseline until the end of the experiment *(Fig. 1)*. Q_t was

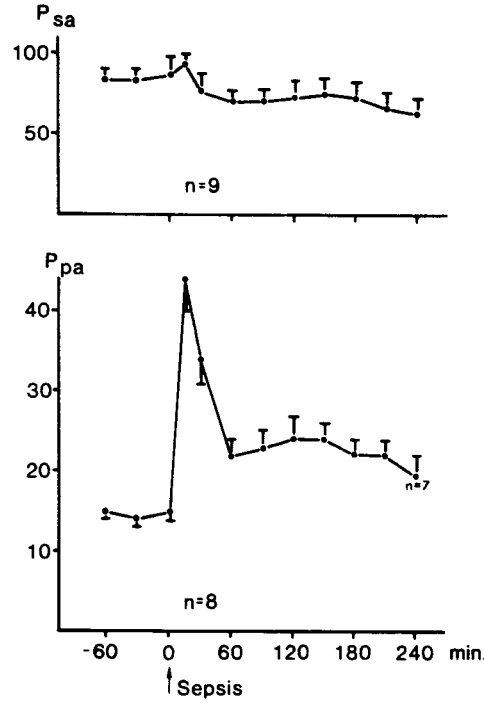

Fig. 1. Mean arterial pressure (P_{sa}) and mean pulmonary arterial pressure (P_{pa}) before and after infusion of live E. coli *bacteria 10^9 kg^{-1} bw. Values are mean±SEM, n=number of animals. P_{sa} was significantly decreased from 60 minutes after bacterial infusion until the end of experiment, compared to presepsis, P_{pa} was significantly increased from 15 minutes until 210 minutes after bacterial infusion, compared to preseptic values.*

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Table 1

Arterial Blood Gases and Cardiac Output Before and After Infusion of *E. coli*

	Minutes after bacterial infusion					
	0	30	60	120	180	240
Q_t ml kg^{-1}bw	119±5	65±5* n=8	84±8* n=7	87±5*	57±6*	45±4*
P_aO_2 kPa	11.2±0.4	8.7±0.5	8.9±0.7	8.3±0.7	8.5±0.8	9.7±0.8 n=6
P_aCO_2 kPa	4.8±0.1	4.6±0.2	4.4±0.1	4.2±0.2	3.6±0.1 n=8	3.7±0.3 n=5
pH	7.40±0.01	7.40±0.01	7.42±0.02	7.43±0.02	7.44±0.02	7.42±0.03 n=6

Values are means ± SEM; n=9. Q_t, cardiac output; P_aO_2, arterial O_2 tension; P_aCO_2, arterial CO_2 tension. *Significantly different from baseline at $P<0.05$. 1 torr(mmHg) = 0.133 kPa.

Table 2

Hematocrit, Leukocyte, and Platelet Count Before and After Infusion of *E. coli*

	Minutes after bacterial infusion				
	0	30	60	120	180
Hematocrit	24.6±1.7	30.3±1.8*	28.9±1.7*	29.7±1.9*	31.8±2.3*
Leukocytes 10^9L^{-1}	6.6±1.1	1.6±0.4*	0.9±0.2*	0.8±0.1* n=7	0.9±0.2* n=7
Platelets 10^9L^{-1}	389±49	369±44	318±41*	336±49 n=7	250±46* n=7

Values are mean ± SEM; n=9. *Significantly different from baseline at $P<0.05$.

119±5ml kg^{-1} min^{-1} during baseline and then decreased significantly after infusion of bacteria and was 65±5 after 30 minutes and at the end of the experiment 45±4ml kg^{-1} min^{-1} *(Table 1)*. PaO_2 and $PaCO_2$ were within normal limits during baseline at 11.2±0.4 and 4.8±0.1kPa respectively. After induction of sepsis PaO_2 as well as $PaCO_2$ decreased significantly and PaO_2 was after 30 minutes 8.7±0.5 and $PaCO_2$ after 60 minutes 4.4±0.1kPa. $PaCO_2$ stayed low throughout the experiment, whereas PaO_2 after 4 hours in 6 sheep was no longer different from baseline at 9.7±0.8. pH was around 7.4 throughout the experiment *(Table 1)*.

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Hematologic parameters

Hct increased significantly from 24.6±1.7 to 30.3±1.8 after 30 minutes and then stabilized. Leukocyte and platelet counts were within normal limits during the baseline period at 6.6±1.1 and 389±49 10^9L^{-1} respectively. After induction of sepsis leukocytes decreased dramatically and were already after 30 minutes 1.6±0.4 10^9L^{-1} and remained low. The platelets decreased more slowly and were after 3 hours 250±46 10^9 L^{-1}, which was significantly decreased compared to baseline *(Table 2)*.

Lymph data

The lymph to plasma protein concentration ratio (L/P) for total protein was 0.62±0.02 in lung lymph during baseline and was significantly decreased compared to baseline between 60 and 120 minutes to the lowest value after 60 minutes of 0.47±0.04. At the end of experiment L/P for total protein was 0.70±0.04 which was not different from baseline values *(Fig. 2)*. L/P for total protein in

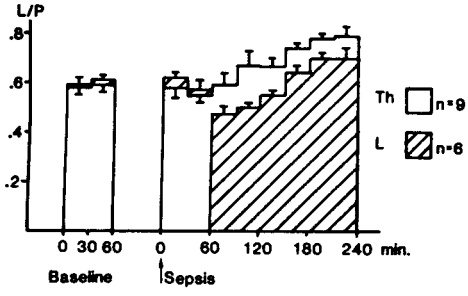

Fig. 2. Lymph to plasma concentration ratio for total protein (L/P) in thoracic duct lymph (n=9) and lung lymph (n=6) during baseline and after infusion of live E. coli *bacteria. Values are mean±SEM. L=lung lymph. Th=thoracic duct lymph. L/P for total protein in L was significantly decreased compared to baseline at 60, 90, and 120 minutes after bacterial infusion. L/P for total protein in Th was significantly increased compared to baseline from 120 minutes until the end of the experiment. L/P for total protein in Th was significantly different from L/P in L at 90, 120, 150, and 180 minutes after bacterial infusion.*

thoracic lymph was at baseline 0.56±0.03 and successively increased during the experiment and was at the end 0.78±0.04. Between 90 and 180 minutes after sepsis, L/P in thoracic lymph was significantly higher than in lung lymph *(Fig. 2)*.

The mean lymph flow in the sheep with thoracic duct fistula was 34.2±6ml/30 minutes. The baseline lung flow in the whole group was 2.3±0.5ml/30 minutes *(Fig. 3)*.

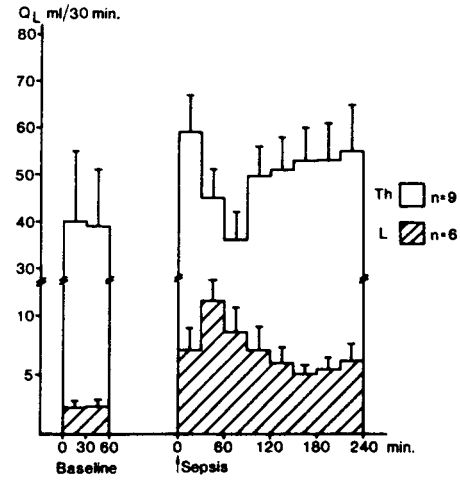

Fig. 3. Thoracic duct lymph flow in 9 and lung lymph flow in 6 out of 9 sheep during baseline and after infusion of live E. coli *bacteria bw. Values are mean±SEM. L=lung lymph. Th=thoracic duct lymph. The lung lymph flow increased significantly during the first 30 minutes after bacterial infusion and was increased over baseline throughout the experiment. The thoracic duct lymph flow was significantly increased over baseline during the first 30 minutes and between 90 and 240 minutes after bacterial infusion.*

After infusion of bacteria the lung lymph flow increased and peaked after 60 minutes at 11.2±2.4ml/30 minutes or 410%±51 over baseline. The flow then decreased and leveled around 5.5ml/30 minute *(Fig. 3)*. The thoracic lymph flow showed a biphasic pattern. The flow was maximal after 30 minutes at 58.3±9ml/30 minutes and then decreased back to baseline flow after 90 minutes. Thereafter the flow again sharply increased and was at the end of the experiment 55.3±10ml/30 minutes *(Fig. 3)*.

The level of Tx B_2 was low in lung lymph during baseline at 7.3±2.4pg/0.1ml

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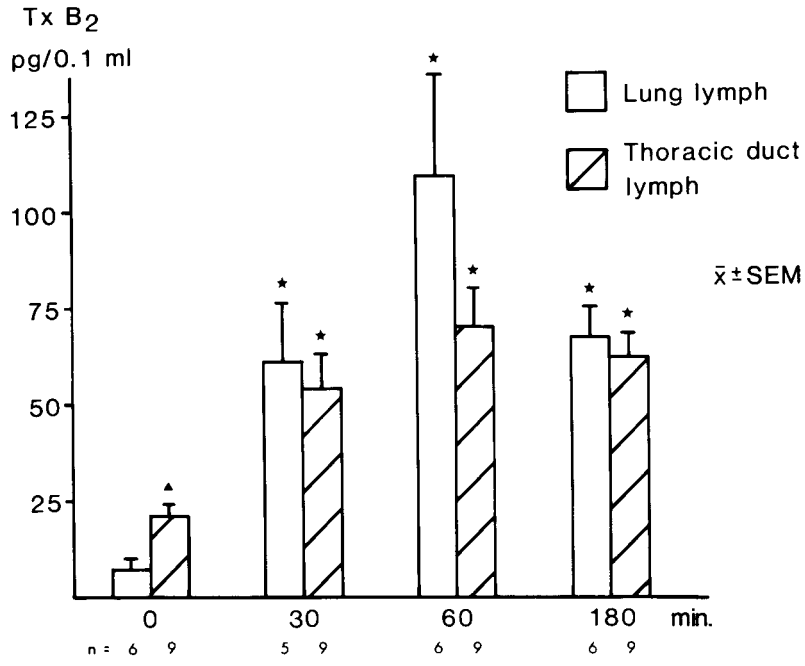

Fig. 4. Thromboxane B_2 (Tx B_2) in thoracic duct and lung lymph during baseline and after infusion of E. coli. *Tx B_2 increased sigificantly in both thoracic duct and lung lymph and remained elevated. Tx B_2 was higher in thoracic duct lymph during baseline, but no differences were seen after bacterial infusion. Values are expressed as x±SEM, n=number of animals. *Significantly different from baseline at p<0.05.*
ΔSignificant difference between thoracic duct and lung lymph at p<0.05.

and increased after bacterial infusion to a peak value after 60 minutes of 109±26pg/0.1ml. Tx B_2 in lung lymph was significantly elevated throughout the experiment after bacterial infusion. In thoracic duct lymph Tx B_2 was 21±3pg/0.1ml during baseline, which was significantly more than in lung lymph. After sepsis Tx B_2 increased to the highest value after 60 minutes of 70±9pg/0.1ml. Tx B_2 stayed significantly elevated in thoracic duct lymph throughout the experiment with no difference compared to lung lymph after infusion of bacteria *(Fig. 4)*. 6-keto was low during baseline in both thoracic duct and lung lymph. There was a significant increase in the concentration of 6-keto at 60 and 180 minutes after sepsis in both thoracic duct and lung lymph but no differences in concentration between the two kinds of lymph *(Fig. 5)*.

DISCUSSION

Combined simultaneous monitoring of lung lymph and thoracic duct lymph flow and composition during various experimental conditions may be a valuable experimental tool. Regional differences in local release and activation of, for example, eicosanoid products and products of the blood proteolytic cascade systems can be studied. Regional events in the lungs may thus be differentiated from systemic reactions. Previous studies have indicated specific local pulmonary reactions to occur during septicemia (4,5).

Release of toxic substances from the gastrointestinal tract during septicemia, transported in thoracic duct lymph, may have a deleterious effect on the experimental animal. However, when thoracic duct lymph was drained in the present

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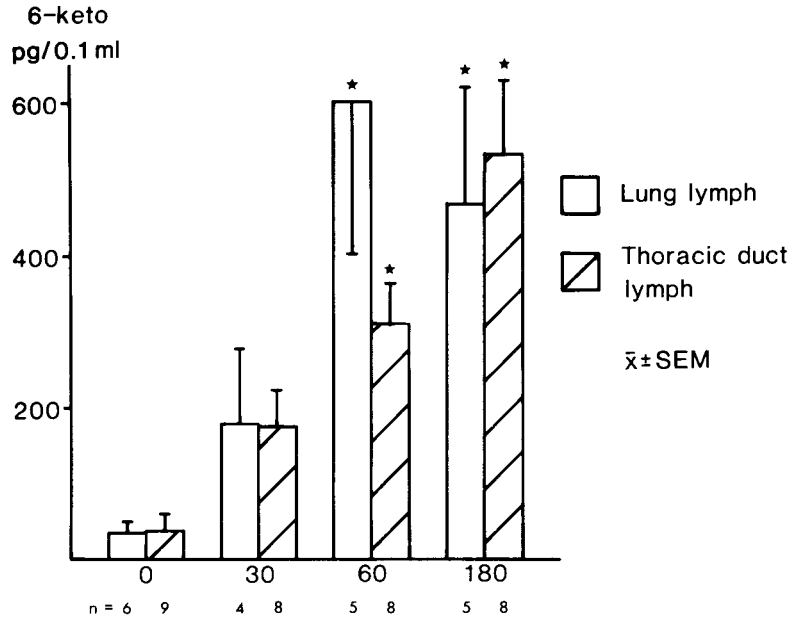

Fig. 5. 6-keto PGF$_I$ (6-keto) in thoracic duct and lung lymph during baseline and after infusion of E. coli. *6-keto increased in both thoracic duct and lung lymph after 60 minutes and remained elevated. There were no differences between thoracic duct and lung lymph concentrations. Values are expressed as x̄±SEM, n=number of animals. *Significantly different from baseline at p<0.05.*

study, the sheep developed similar hemodynamic and respiratory reactions as septic sheep in this laboratory that only had a lung lymph fistula (12). Because of the similarity of responses, it seemed unlikely that the thoracic duct contained substances that alter the pathophysiology following bacterial infusion, although this aspect was not tested directly. The changes in P_{sa}, Q_t, P_{pa}, and P_aO_2 were similar between septic sheep with or without thoracic duct lymph drainage. P_{sa} and Q_t decreased significantly during the first hour and then stabilized on a low level. P_{pa} increased during bacterial infusion and peaked after 30 minutes. Thereafter the pressure decreased but remained elevated over baseline. P_aO_2 decreased during the first 30 minutes after bacterial infusion and then remained low. The reactions of leukocytes, platelets, and Hct were also similar with leukopenia, thrombocytopenia, and hemoconcentration in the septic sheep. The combination of high lung lymph flow with increased or unchanged L/P for total protein also indicated increased pulmonary vascular permeability as in previous experiments (2-4,12). In other experiments from this laboratory septic sheep following infusion of live *E. coli* were found to have increasing permeability of the lung microvascular membrane (14). In these experiments the osmotic reflection coefficient of the pulmonary microvessels for total protein declined from 0.76 to 0.54 after the septic insult. In the present study the pulmonary hydrostatic pressure was not elevated to achieve a filtration independent state. Thus, an evaluation of permeability disturbances was not possible.

Thoracic duct lymph is composed of lymph from many organs but mainly the liver and intestinal tract. The capillaries of the liver are considered leaky with a reflection coefficient close to 0 whereas the fenestrated capillaries of the intestine have the same sieving capacity as the pulmonary microvessels with a reflection coefficient approaching 1 (15,16).

The biphasic flow pattern that was noted in thoracic duct lymph after the

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septic insult has been described by Alikan and Hardy (17) in septic shock in dogs. They simultaneously studied thoracic duct, liver and intestinal lymph flow. After infusion of endotoxin, liver lymph flow increased but returned to baseline within 15-20 minutes. This increased liver lymph flow coincided with portal hypertension and was abolished with diversion of portal blood flow around the liver. The intestinal lymph flow increased, when liver lymph flow and portal pressure were declining or had returned to baseline, and stayed elevated during the observation period for several hours. During the phase of increased intestinal lymph flow portal pressure was normal. This extrahepatic portal response could have been due to either increased microvascular permeability or an increased surface area. Thoracic duct lymph flow was in this experiment biphasic corresponding to the changes in liver and intestinal lymph flow. It can only be speculated that the increased lymph flow from the intestines through the thoracic duct was the effect of increased permeability of the intestinal microvessels. Earlier experiments have shown increased amounts of lysosomal enzymes and 5-HT after sepsis in the thoracic duct that could have exerted a toxic effect on the microvessels (6,18).

Because we attempted to keep conditions identical to previous experiments from this laboratory (except for the thoracic duct fistula), no laparotomy was performed. Thus, no recordings of portal pressure levels were possible. Nonetheless, portal pressure was likely elevated during sepsis (17). High lymph flow coupled with maintained or high L/P have often been considered as indicative of increased microvascular permeability. However, an increased microvascular exchange surface area (e.g., increased capillary blood flow) may yield an identical pattern. To differentiate between increased surface area and altered microvascular permeability analysis of lymph, data needs to be done at maximal lymph flows when L/P is filtration independent (14,19,20). Thus, the addition of portal pressure measurement would not have shed further light on this issue since filtration independence of L/P was not done.

Drake et al (21) found that Q_L was affected by the height of the outflow cannula connected to the lymph vessel, and, during sepsis, also by the resistance in the cannula. Q_L was reduced as the outflow cannula was elevated and during sepsis the resistance in the cannula was flow limiting and Q_L decreased by 50%. However, the changes in Q_L did not affect the L/P total protein ratio indicating that lung lymph protein values reflected changes in the capillary although not the true filtration rate. Nonetheless, in the present experiment and in other protocols from this laboratory using awake sheep, the height of the outflow cannula was constant and unchanged. This constancy permits comparison of results during baseline with sepsis although the full magnitude of increase in filtration rate may not be entirely accurate.

Increasing levels of Tx B_2 and 6-keto have been found in lung lymph after a septic insult (4,22) with unchanged levels in prefemoral lymph (4) and a transpulmonary blood gradient of Tx B_2 and 6-keto suggesting local pulmonary release (22). Tx B_2 and 6-keto levels in lung lymph are increased only for two hours after endotoxemia, but after a lethal dose of endotoxin high levels persist (4). A previous study demonstrated that after infusion of live bacteria, high levels of Tx B_2 and 6-keto are found in lung lymph (5) similar to the findings in the present experiment. Increasing levels of Tx B_2 and 6-keto are also found in thoracic duct lymph, however, after bacterial infusion, suggesting increased release or decreased degradation within the gastrointestinal tract. Together these studies demonstrate that increased lymph levels of Tx B_2 and 6-keto are not just a local pulmonary response to sepsis.

Demling et al (23) simultaneously monitored lung lymph and prefemoral lymph in the awake sheep. After endo-

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toxemia femoral lymph flow was unchanged but lung lymph flow increased with increasing L/P suggesting increased pulmonary microvascular permeability in the lungs. After a local burn injury in the same experimental model there was no change in pulmonary permeability whereas the prefemoral lymph findings suggested increased microvascular permeability in the burned area. These divergent responses in different capillary beds stress the need to monitor different body regions simultaneously as done in our experiments.

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Lennart Smith, M.D., Ph.D.
Department of Surgery
Sahlgrenska sjukhuset
S-413 45 Göteborg, SWEDEN

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