Diuretics, hepatic and thoracic duct lymph flows in the dog

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Summary
1. Simultaneous thoracic duct and hepatic lymph flows were measured in 29 mongrel dogs before and after the intravenous administration of mannitol, ethacrynic acid, frusemide and chlorothiazide in separate experiments.

2. Thoracic duct lymph flow increased significantly after each diuretic agent was administered.

3. Hepatic lymph flow increased only after ethacrynic acid and mannitol administration. Frusemide and chlorothiazide did not alter hepatic lymph flow.

4. These data show that increases in thoracic duct lymph flow after ethacrynic acid and mannitol arise partly from the liver, as well as from other organs.

Key words: liver, transcapillary fluid movement, transcapillary protein movement.

Introduction
The intestinal tract and the liver are considered to be the major source of lymph flow in the thoracic duct under basal conditions (Ruznyak, Foldi & Szabo, 1960). Increases in thoracic duct lymph flow have been reported in dogs after injection of mannitol (O’Morchoe & O’Morchoe, 1967), ethacrynic acid (Szwed, Hamburger & Kleit, 1971), and frusemide and chlorothiazide (Szwed, Kleit & Hamburger, 1972). A major source of this increased thoracic duct lymph flow has been shown to be the intestinal tract (Szwed, Maxwell, Elliott & Redlich, 1977). The present studies were performed to assess the contribution of the liver to increased thoracic duct lymph flow after diuretic administration.

Methods
A total of 29 mongrel dogs (10–20 kg), kept without food for 1 day, were anaesthetized with sodium pentobarbital (30 mg/kg body wt.). Only one experiment was performed in each animal. All animals were intubated and ventilated with a Harvard respirator. The thoracic duct was identified at its entry into the venous system in the neck and ligated. A midline abdominal incision was then made to expose the main hepatic lymphatics, the largest of which was cannulated with polyethylene tubing with an internal diameter of 0.5 mm and an external diameter of 0.96 mm. The catheter was exteriorized through a stab wound in the abdominal wall and the abdomen closed. The thoracic duct was then cannulated with tubing of the same size as that used for the hepatic lymphatic system and the dog treated with 2000 units of aqueous heparin to prevent lymph clotting.

Arterial blood pressure was monitored via a catheter in the right femoral artery, by using a strain-gauge pressure transducer and a Beckman Dynograph type RS recorder. A catheter was inserted into the left femoral vein, advanced into the inferior vena cava and connected to a saline manometer to monitor inferior vena caval pressure.
Seven dogs were given mannitol, nine ethacrynic acid, seven frusemide, and six chlorothiazide. At 30 min after the surgical procedures, observations were made until lymph flows in both thoracic and hepatic lymph ducts were consistent during three consecutive 10 min periods. The mean of three consecutive periods before injection of the drug was used as control lymph flow. Likewise, the mean of three consecutive periods after injection of the drug was employed as the experimental lymph flow. All drugs were administered as bolus injections. One diuretic agent was then administered in each experiment: the dose of mannitol was \(0.5 \text{ g/kg (0.0027 mol/kg)}\) body weight, and that of ethacrynic acid \(4-5 \text{ mg/kg (0.013-0.016 mmol/kg)}\). Frusemide and chlorothiazide were given in doses of \(8-10 \text{ mg/kg (0.02-0.03 mmol/kg)}\) and \(20-25 \text{ mg/kg (0.06-0.08 mmol/kg)}\) respectively. These doses were those employed in previous studies of thoracic duct lymph flow.

Lymph flows, arterial blood pressure and inferior vena caval pressure were measured at the end of each 10 min period, during the control and experimental condition. Sodium and potassium concentrations were measured in blood and lymph samples by flame photometry with lithium as an internal standard, and total protein concentration by the biuret method. Each animal served as its own control. Statistical analysis of the data was carried out by using one-way analysis of variance. Values are given as mean ± SE.

**Results**

The flow of lymph from the thoracic duct increased significantly \((P < 0.01)\) after each drug was administered. The increase in lymph flow ranged from 46% with mannitol to 55% with ethacrynic acid (Table 1). There were no significant inter- or intra-group differences in thoracic duct lymph flow between the four drugs studied. The average duration of increased thoracic duct lymph flow was 45 min. Hepatic lymph flow was increased by mannitol \((P < 0.05)\) and ethacrynic acid \((P < 0.01)\). With both drugs hepatic lymph flow increased for an average of 1 h. Frusemide and chlorothiazide caused no change in hepatic lymph flow (Table 1). Fig. 1 shows the flow of lymph from the thoracic and hepatic lymph ducts in a representative experiment. No changes occurred in mean arterial pressure or inferior vena caval pressure during the studies (Table 1).

No changes in sodium, potassium or total protein concentration occurred in either thoracic duct or hepatic lymph or plasma: neither were there any changes in the ratios of concentrations of protein in thoracic duct or hepatic lymph and plasma (Table 2).

**Discussion**

Increases in thoracic duct lymph flow have been reported after the administration of several chemically unrelated diuretic agents. Increases of 600% above control have been observed in thoracic duct flow after the injection of a mannitol solution to dogs (O'Morchoe & O'Morchoe, 1967). Increases of 145–417% above control flows occurred after meralluride in intact dogs (Patterson & Ray, 1964). Thoracic duct lymph flow has been shown to increase from 64 to 105% above control

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**Table 1. Summary of lymph flow and haemodynamics with mannitol, ethacrynic acid, chlorothiazide, and frusemide**

Values are expressed as means ± SEM. C, Control state; E, experimental state; IVCP, inferior vena caval pressure; MAP, mean aortic pressure; n, number of studies; N.S., not significant.

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Thoracic lymph flow (ml/min)</th>
<th>Change (%)</th>
<th>n</th>
<th>Hepatic lymph flow (ml/min)</th>
<th>Change (%)</th>
<th>n</th>
<th>MAP (mmHg)</th>
<th>n</th>
<th>IVCP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>C</td>
<td>7 0.47 ± 0.10</td>
<td>+46%</td>
<td>7</td>
<td>0.09 ± 0.04</td>
<td>+33%</td>
<td>7</td>
<td>97 ± 4</td>
<td>7</td>
<td>5.7 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>7 0.69 ± 0.13</td>
<td></td>
<td>7</td>
<td>0.12 ± 0.05</td>
<td></td>
<td>7</td>
<td>99 ± 7</td>
<td>7</td>
<td>5.9 ± 0.7</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td>C</td>
<td>9 0.43 ± 0.08</td>
<td></td>
<td>8</td>
<td>0.12 ± 0.04</td>
<td></td>
<td>9</td>
<td>108 ± 4</td>
<td>9</td>
<td>5.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>9 0.69 ± 0.26</td>
<td>+55%</td>
<td>8</td>
<td>0.17 ± 0.12</td>
<td>+42%</td>
<td>9</td>
<td>108 ± 4</td>
<td>9</td>
<td>5.3 ± 0.5</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>C</td>
<td>6 0.61 ± 0.15</td>
<td></td>
<td>6</td>
<td>0.17 ± 0.03</td>
<td></td>
<td>6</td>
<td>122 ± 14</td>
<td>6</td>
<td>5.2 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>6 0.95 ± 0.27</td>
<td>+54%</td>
<td>6</td>
<td>0.16 ± 0.03</td>
<td>-5%</td>
<td>6</td>
<td>121 ± 12</td>
<td>6</td>
<td>5.1 ± 0.5</td>
</tr>
<tr>
<td>Frusemide</td>
<td>C</td>
<td>7 0.37 ± 0.05</td>
<td></td>
<td>7</td>
<td>0.11 ± 0.04</td>
<td></td>
<td>7</td>
<td>117 ± 11</td>
<td>7</td>
<td>5.5 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>7 0.58 ± 0.04</td>
<td>+59%</td>
<td>7</td>
<td>0.11 ± 0.04</td>
<td>0%</td>
<td>7</td>
<td>115 ± 6</td>
<td>7</td>
<td>4.4 ± 0.7</td>
</tr>
</tbody>
</table>
values after injection of ethacrynic acid (Szwed et al., 1971), frusemide and chlorothiazide (Szwed et al., 1972) in intact as well as in anephric animals. However, the organs of origin of the lymph have not been defined previously. Studies in our laboratory have shown that the intestinal tract is a major contributor to increased thoracic duct lymph flow after mannitol and ethacrynic acid and frusemide administration (Szwed et al., 1977). These same studies showed no increases in intestinal lymph flow after chlorothiazide administration.

Increases in lymph flow occur as a result of alterations in Starling's forces which favour net filtration. Since arterial blood pressure was unchanged in our studies, the increases in lymph flow observed were unlikely to have resulted from decreases in precapillary vascular resistance. Likewise, venous pressure was not elevated, suggesting that increases in postcapillary resistance leading to increased capillary filtration were not the cause of the increased lymph flow. Neither plasma nor hepatic lymph protein concentrations were altered after diuretic administration, indicating the absence of changes in tissue oncotic pressures to account for the increased lymph flow. Tissue pressure was not measured but it is unlikely that this was altered by the diuretics. Therefore, Starling's forces were not altered measurably by the administration of diuretics in this study. Hence changes in capillary permeability or surface area seem the most likely causes for the increased hepatic lymph flow

![Graph showing lymph flow](image)

**Fig. 1.** Simultaneous measurements of thoracic duct lymph flow (●) and hepatic lymph flow (○) were made before and after administration of ethacrynic acid (arrow).
observed after ethacrynic acid. However, the contribution of each of these two factors to cause increased lymph flow from the liver cannot be ascertained from this study.

Mannitol expands extracellular volume at the expense of intracellular water. Therefore, the increased hepatic lymph flow after the administration may be explained by its ability to expand the extracellular water compartment, i.e. interstitial water, and hence enhance lymph flow by a net osmotic extraction of water from the intracellular compartment of the liver cells.

The different effects of various diuretics on hepatic lymph flow may have resulted from different responses at the receptor site. Ethacrynic acid is an aryloxyacetic acid derivative whereas both frusemide and chlorothiazide are benzothia diazine derivatives. The differences in chemical structures could account for the differences in lymph flow observed.

It is probable, from our studies and those of Dikshit, Vyden, Forrester, Chatterjee, Prakash & Swann (1973), that the common clinical problem of liver congestion produced by cardiac failure may be alleviated by ethacrynic acid partly through an increase in hepatic lymph flow. The full implications of the usefulness of diuretics in clinical medicine are only beginning to be known.

References