Protein Content in Lymph and Edema Fluids in Congestive Heart Failure

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SUMMARY
Protein content of tissue fluid and lymph is not uniform and depends upon regional differences in capillary permeability modified by changes in capillary filtration pressure. Whereas increased pressure in freely permeable liver sinusoids promotes formation of excess liver and thoracic duct lymph and ascitic fluid high in protein, increased venous pressure in less permeable beds promotes formation of excess lymph and edema fluid progressively lower in protein content. To ascertain the influence of colloid oncotic pressure on excess lymph and edema formation in congestive heart failure, a disorder characterized by generalized venous hypertension, protein content of lymph (thoracic duct, liver, and small intestine), intracavitary and peripheral edema fluid, and plasma were measured in 42 patients with cardiac failure. In “acute” heart failure, thoracic duct lymph and ascitic fluid have high protein content (85% and 68% of plasma protein respectively) and are derived primarily from the liver, but in “chronic” heart failure protein content of thoracic duct lymph and ascitic fluid are lowered (46% and 40% of plasma protein respectively) by lymph from extrahepatic sites. In both stages, pleural and leg edema fluid are comparatively low in protein content (26 to 44% and 3 to 8% of plasma protein respectively).

In congestive heart failure, edema and intracavitary fluid form primarily in response to increased venous pressure which outside the liver is partially counterbalanced by increased effective plasma oncotic pressure.

Additional Indexing Words:
Ascites Pleural effusion Heart failure Protein Oncotic pressure

THE PARTITION of extracellular fluid between blood and tissues is determined primarily by the balance of hydrostatic and oncotic pressure gradients across capillary membranes.1,2 A small excess of tissue fluid normally forms, enters lymphatics, and returns to the blood stream.3 However, the amount and composition of excess tissue fluid or lymph is not uniform throughout the body and depends not only on “Starling forces” but also on regional differences in capillary permeability. Thus, highly permeable hepatic sinusoids produce a lymph that is almost as high in protein content as plasma, whereas the less permeable limb capillaries form lymph that is low in protein.7 Furthermore, venous hypertension that results from restriction to

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venous blood flow not only increases filtration pressure and formation of lymph, but further exaggerates regional differences in protein content of lymph.\textsuperscript{8,9} It is ultimately the effective colloid osmotic (oncotic) pressure of plasma (plasma minus tissue) that counterbalances the effective filtration pressure.\textsuperscript{10}

In congestive heart failure, venous return is impeded and venous pressure and volume increase. Accordingly, filtration of fluid out of capillaries into tissues is favored and production of lymph increases.\textsuperscript{11,12} Although the complex derangements leading to edema formation in this disorder are not clearly understood, a satisfactory explanation must encompass regional differences in capillary fluid fluxes and in lymph drainage.

On the basis of these considerations, protein content in lymph and edema fluids was measured in patients with cardiac failure in an attempt to determine the effective plasma oncotic pressure and the influence of capillary hydrostatic pressure on production of excess interstitial fluid in congestive heart failure. Total protein content of thoracic duct, liver and intestinal lymph, peritoneal, pleural, and peripheral edema fluid and plasma was measured in various combinations in 42 patients with varying severity and duration of cardiac decompensation. The results were compared with findings in control subjects and with previous observations in patients with hepatic cirrhosis in whom venous hypertension is confined to the splanchnic bed, a great excess of thoracic duct lymph is formed, and ascites is a common occurrence.

### Methods

Forty-two patients with existing or prior cardiac failure were studied (table 1). Each patient was under treatment in the hospital or had been treated for congestive heart failure previously. Observations were made in 17 living patients, including three with "compensated" cardiac failure, and in 25 others at autopsy. The etiology of cardiac failure varied but the predominant causes were arteriosclerotic and rheumatic heart disease. Ages ranged from 4 weeks to 88 years.

Eighteen patients who died within 3 weeks after onset of symptoms were categorized as "acute" cardiac failure. Each patient was receiving digitalis therapy, and 14 of them were being treated with diuretic drugs at the time of death.

Twenty-one patients who had signs and symptoms of cardiac decompensation for several months to several years were classified as "chronic" congestive heart failure. They had been eating a salt-restricted diet and had been receiving continuous medication, including digitals and diuretic drugs. Thirteen patients had central venous pressure determinations while in cardiac failure; the mean value was 32 cm of saline and the median 27 cm of saline. In 19 of the patients the functional and therapeutic classification was IV-E.

Three patients had "compensated" heart failure. None had visible edema and functional-therapeutic classification ranged from I-A to II-B. Each patient was receiving digitalis and two were receiving diuretic drugs as well.

Total protein content in lymph, ascitic, pleural and peripheral edema fluid, and plasma was measured in a T/S refractometer (American Optical Model 10401) or by the biuret method. Small samples of lymph were collected in heparinized capillary tubes after transection of a lymphatic vessel. Peripheral edema fluid was similarly collected spontaneously or during gentle compression after insertion of a fine needle into

### Table 1

<table>
<thead>
<tr>
<th>Type of heart disease</th>
<th>No. of patients</th>
<th>Sex</th>
<th>Age in years (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriosclerotic</td>
<td>21</td>
<td>Male: 10 Female: 11</td>
<td>Male: 68 Female: 75</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>10</td>
<td>Male: 3 Female: 7</td>
<td>Male: 42 Female: 49</td>
</tr>
<tr>
<td>Congenital</td>
<td>4</td>
<td>Male: 3 Female: 1</td>
<td>Male: 11 Female: 47</td>
</tr>
<tr>
<td>Cor pulmonale</td>
<td>4</td>
<td>Male: 3 Female: 1</td>
<td>Male: 59 Female: 45</td>
</tr>
<tr>
<td>Marie-Strümpel spondylitis (aortic insufficiency)</td>
<td>1</td>
<td>Male: 1 Female: 0</td>
<td>Male: 51 Female: -</td>
</tr>
<tr>
<td>Idiopathic cardiomyopathy</td>
<td>1</td>
<td>Male: 1 Female: 0</td>
<td>Male: 45 Female: -</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>Male: 0 Female: 1</td>
<td>Male: - Female: 47</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>21/21</td>
<td>46/53</td>
</tr>
</tbody>
</table>
PROTEIN CONTENT IN LYMPH AND EDEMA FLUIDS

Figure 1

Total protein in thoracic duct lymph (mean ± SD) in control subjects and in patients with acute, chronic, and compensated congestive heart failure (CHF). Numbers at the bottom of each bar represent number of patients studied.

The edematous leg. In 15 patients the thoracic duct in the left side of the neck was cannulated under local anesthesia for therapeutic purposes, and lymph flow rate (by gravity drainage) and total protein content were determined. These cases were reported in detail previously. In two of the patients leg edema fluid was sampled and total protein content determined.

In 25 patients at autopsy, samples of thoracic duct lymph from the posterior mediastinum (16 patients), liver lymph from perportal lymphatics (17 patients), intestinal lymph from mesenteric lacteals (9 patients), pleural fluid from right (14 patients) and left (9 patients) thoracic cavities, ascitic fluid (22 patients), leg edema fluid (4 patients) and plasma (25 patients) were obtained and total protein content was measured. In 78 samples the albumin level was determined by Micro Zone electrophoresis (Beckman Model R100, 110) or by salt fractionation. The findings were compared with values in lymph and plasma at operation or autopsy in control subjects without congestive heart failure or hepatic cirrhosis.

Results

Figures 1 to 3 summarize the total protein content (expressed as % plasma level) in lymph and edema fluids in patients with "acute," "chronic," and "compensated" congestive heart failure. Total protein levels in lymph of control subjects are shown in figures 1 and 2.

In patients with "acute" congestive heart failure, the protein level in thoracic duct lymph was 15% higher than control values (P < 0.01) and within normal limits in liver and intestinal lymph* (figs. 1 and 2). The protein content in ascitic fluid was very high (68% of plasma protein), lower in right and left pleural fluid (44% and 35% of plasma protein respectively), and very low in leg edema fluid (3% of plasma protein; fig. 3).

*No difference was found in control protein levels in thoracic duct, liver, and intestinal lymph obtained at operation or at autopsy as reported previously.13

Figure 2

Total protein in liver and intestinal lymph (mean ± SD) in control subjects and in patients with acute and chronic congestive heart failure (CHF). Numbers at the bottom of each bar represent number of patients studied.

Figure 3

Total protein in ascitic, pleural, and peripheral edema fluid in acute and chronic congestive heart failure (CHF). Numbers on the bottom of each bar represent number of patients studied.
Table 2
Average Levels of Albumin (A) and Globulin (G) in Plasma and Lymph (g/100 ml) Based on the Total and Fractional Protein Content in Patients with “Acute,” “Chronic,” and “Compensated” Congestive Heart Failure (CHF) Compared with Control Subjects*

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>“Acute” CHF</th>
<th>“Chronic” CHF</th>
<th>“Compensated” CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%A</td>
<td>A/G</td>
<td>%A</td>
<td>A/G</td>
</tr>
<tr>
<td>Total protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
<td>6.6</td>
<td>57.0</td>
<td>3.76</td>
<td>3.67</td>
</tr>
<tr>
<td>(11)</td>
<td>2.84</td>
<td></td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td>Thoracic duct lymph</td>
<td>4.3</td>
<td>59.0</td>
<td>2.70</td>
<td>3.10</td>
</tr>
<tr>
<td>(10)</td>
<td>1.60</td>
<td></td>
<td>(6)</td>
<td></td>
</tr>
<tr>
<td>Liver lymph</td>
<td>6.2</td>
<td>64.2</td>
<td>3.98</td>
<td>4.20</td>
</tr>
<tr>
<td>(2)</td>
<td>2.22</td>
<td></td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>Intestinal lymph</td>
<td>4.1</td>
<td>62.3</td>
<td>2.55</td>
<td>2.39</td>
</tr>
<tr>
<td>(2)</td>
<td>1.55</td>
<td></td>
<td>(3)</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses represent the number of subjects whose data have been averaged for the value tabulated.

Table 3
Average Levels of Albumin (A) and Globulin (G) in Ascitic, Pleural, and Leg Edema Fluid (g/100 ml) Based on the Total and Fractional Protein Content in Patients with “Acute” and “Chronic” Congestive Heart Failure (CHF)*

<table>
<thead>
<tr>
<th></th>
<th>“Acute” CHF</th>
<th>“Chronic” CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%A</td>
<td>A/G</td>
</tr>
<tr>
<td>Ascitic fluid</td>
<td>5.7</td>
<td>48.7</td>
</tr>
<tr>
<td>(9)</td>
<td></td>
<td>(3)</td>
</tr>
<tr>
<td>Right pleural fluid</td>
<td>3.6</td>
<td>57.2</td>
</tr>
<tr>
<td>(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left pleural fluid</td>
<td>2.4</td>
<td>50.5</td>
</tr>
<tr>
<td>(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg edema fluid</td>
<td>0.3</td>
<td>58.0</td>
</tr>
<tr>
<td>(2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Numbers in parentheses represent number of subjects whose data have been averaged for the value tabulated.

In patients with “chronic” congestive heart failure, the protein content in thoracic duct lymph was 36% lower (P < 0.01) and in intestinal lymph 31% lower (P < 0.02) than control values and within normal limits in liver lymph (figs. 1 and 2). The protein content in ascitic fluid and right pleural fluid was 41% lower (P < 0.01 and P < 0.02 respectively) than values in “acute” heart failure, but the protein level in leg edema and left pleural fluid was not significantly different (P > 0.4 and P > 0.2 respectively) from values in “acute” heart failure (fig. 3).

In patients with “compensated” congestive heart failure, the protein level in thoracic duct lymph was within normal limits (fig. 1).

Tables 2 and 3 represent the average levels of albumin and globulin in plasma, lymph, and edema fluids in patients in congestive heart failure as compared with control subjects. The albumin fraction was lower in patients with heart failure but there were no
PROTEIN CONTENT IN LYMPH AND EDEMA FLUIDS

Table 4

Estimated Oncotic Pressure (II in mm Hg) in Plasma (II P), Liver (II L), Extrahepatic Portal (II e) and Peripheral Tissues (II L) in Control Patients and in Those with "Acute" and "Chronic" Congestive Heart Failure (CHF) Calculated from Albumin and Globulin Concentrations (g%) in Plasma, Liver Lymph, Intestinal Lymph, and Peripheral Interstitial Fluid (Tables 2 and 3).

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>“Acute” CHF</th>
<th>“Chronic” CHF</th>
<th>Effective II P</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>19.6</td>
<td>23.6</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>II L</td>
<td>19.1</td>
<td>26.4</td>
<td>17.4</td>
<td></td>
</tr>
<tr>
<td>II L</td>
<td>11.4</td>
<td>13.6</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>II L</td>
<td>4.8†</td>
<td>0.7</td>
<td>0.8</td>
<td></td>
</tr>
</tbody>
</table>

* Based on van’t Hoff’s law corrected for Donnan effects and protein-protein interaction.14

\[
\begin{align*}
\pi \text{ albumin} &= 2.8c + 0.18c^2 + 0.012c^3 \\
\pi \text{ globulin} &= 1.6c + 0.15c^2 + 0.006c^3 \\
(c &= \text{g}%).
\end{align*}
\]

† Estimated from animals.15

esential differences between the "acute" and "chronic" stages. Note that there is a slight discrepancy between the average values in total protein shown in figures 1 to 3 because not all samples were fractionated for albumin.

Table 4 represents estimated oncotic pressure in the plasma, liver, intestine, and lower extremity in control patients and in those with congestive heart failure. Whereas venous hypertension in heart failure immediately tends to shift fluid into the liver, an increase in effective plasma oncotic pressure in extrahepatic portal and peripheral capillaries requires a rise of at least 4 mm Hg in filtration pressure to produce a net fluid flux into these tissues.

Discussion

Starling recognized the importance of plasma oncotic pressure in regulating capillary fluid exchange; he reasoned further that elevation of capillary hydrostatic pressure would lead to a fall in tissue oncotic pressure: "With increased capillary pressure there must be increased transudation until equilibrium is established at a somewhat higher point, when there is a more dilute fluid in the tissue spaces and therefore a higher absorbing force to balance the increased capillary pressure."11

In general, mild elevations in venous pressure are initially counterbalanced by a reduction in tissue oncotic pressure (table 4), but a further sustained rise in venous pressure shifts fluid into tissues and increases flow of low-protein lymph.8,16 When the rate of formation of capillary filtrate exceeds the rate of lymph reabsorption, low-protein edema fluid accumulates.7,17

The liver, however, does not behave in this fashion. Hepatic sinusoids are perfused primarily by low-pressure portal venous blood and are lined by a very tenuous endothelium with large gaps,18 allowing molecules the size of plasma protein to pass freely.6,18 As a result, there is little or no oncotic gradient across the sinusoidal wall. Small increments in the normally low venous pressure produce a great increase in production of hepatic capillary filtrate and hepatic lymph high in protein.19,20 Accordingly, in dogs with constriction of the inferior vena cava above the diaphragm and in patients with "early" hepatic cirrhosis, restriction to hepatic venous outflow greatly increases flow of high-protein lymph from perportal hepatic lymphatics and the thoracic duct.20,21 When transfer of fluid out of the sinusoid exceeds the capacity of hepatic lymphatics to absorb the fluid, excess liver lymph spills into the peritoneal cavity to form ascitic fluid high in protein.20,21 In contrast, in dogs with an aorto-portal vein shunt combined with restriction to transhepatic portal blood flow, and in patients with far-advanced hepatic cirrhosis, marked elevation in extrahepatic portal pressure (>30 cm of saline) promotes the formation of large
amounts of both mesenteric and thoracic duct lymph very low in protein.\textsuperscript{21, 22} When transfer of fluid out of splanchnic capillaries exceeds the capacity of mesenteric lymphatics to absorb the fluid, excess extrahepatic portal lymph very low in protein accumulates in the peritoneal cavity.\textsuperscript{21, 22}

Failure of the heart to pump blood effectively into the arterial circulation leads to venous hypertension. The delicately balanced liver sinusoid responds with a great outpouring of liver lymph high in protein that floods the thoracic duct. When the formation of excess liver lymph is more rapid than its reabsorption, ascitic fluid high in protein accumulates. (As in caval-constricted dogs, protein values in ascitic fluid are somewhat lower than in liver lymph after osmotic equilibration with interstitial fluid in the extrahepatic portal bed).\textsuperscript{19, 23} On the other hand, venous hypertension outside the liver increases filtration of water more than protein.\textsuperscript{24} When regional lymphatics are overwhelmed, peripheral edema fluid very low in protein and pleural fluid relatively low in protein result.\textsuperscript{4}

Starling believed that in the early stages of heart failure forced outflow of plasma from the venous side of the circulation into the liver substance and its lymphatic network protected the failing heart and at the same time buffered the circulation outside the liver from venous hypertension.\textsuperscript{27} The data suggest, however, that as this compensatory mechanism becomes insufficient, excess lymph can no longer return to central veins with elevated pressure as fast as it forms, and resistance to transhepatic portal blood flow rises. Mesenteric venous hypertension develops, and protein content in extrahepatic portal lymph falls. Protein concentration of thoracic duct lymph also decreases, reflecting the greater contribution of extrahepatic lymph. However, the protein levels in intestinal and thoracic duct lymph and ascitic fluid seldom fall to the very low levels characteristic of far-advanced hepatic cirrhosis in which portal hypertension is much more prominent. The difference in portal circulatory dynamics between cirrhosis and congestive heart failure probably relates to concomitant alterations in splanchnic arterial blood flow. Whereas patients with cirrhosis have normal or increased cardiac output\textsuperscript{29} in conjunction with reduced transhepatic portal blood flow,\textsuperscript{29} patients with heart failure have decreased effective cardiac output\textsuperscript{30, 31} partially offsetting the tendency for portal pressure to rise from increased resistance to transhepatic portal flow.

Controversy exists concerning the mechanism of edema formation in congestive heart failure—that is, does edema result primarily from renal salt and water retention,\textsuperscript{32-36} lymphatic obstruction,\textsuperscript{37} or changes in capillary permeability due to decreased cardiac output and hence arterial perfusion,\textsuperscript{31, 37} or is it a direct result of systemic venous hypertension?\textsuperscript{28, 39} Ischemia or trauma to capillaries as well as lymphatic obstruction alone results in edema fluid that is consistently high rather than low in protein.\textsuperscript{40, 41} Plasma simply “leaks” into tissues in bulk or fails to be removed. Lymph stasis, however, does eventually develop in cardiac failure as lymphatics are overloaded and lymph flow into high pressure central veins is impeded.\textsuperscript{42-45} But the fact that ascitic fluid from the liver is high in protein, and that edema fluid in other areas is low indicates that the primary driving force is venous hypertension resulting from failure of forward venous flow. Retention of salt and water further expands extracellular fluid volume and imposes an ever increasing burden on an already overworked lymphatic circulation. On the other hand, treatment with low-salt diet and diuretic drugs contracts extracellular fluid volume and reduces the load on the lymphatic circulation.

In congestive heart failure, the protein content of lymph and edema fluids reflects the hydrostatic pressure in different capillary beds and allows an estimation of effective plasma
oncotic pressure, a crucial unknown in Starling's law of transcapillary fluid exchange. High-protein ascitic fluid, relatively low-protein pleural fluid and very low protein peripheral edema fluid arise primarily in response to venous hypertension, which favors capillary filtration and eventually impedes lymphatic drainage.

References
41. Ibid, p. 458.
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WILLIAM R. COLE and JOHN R. SMITH

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