Transcapillary Water and Protein Flux in the Canine Intestine with Acute and Chronic Extrahepatic Portal Hypertension

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SUMMARY. Intestinal transcapillary water and total protein flux were determined in dogs with chronic extrahepatic portal hypertension after construction of an aortic-portal shunt combined with hilar portal vein constriction and compared to acute portal vein constriction. Measurements were made of thoracic duct lymph flow, portal venous pressure, and total protein concentration in plasma, thoracic duct lymph, intestinal and liver lymph. From these data and calculations based on the dual visceral origin of thoracic duct lymph from liver and intestine, intestinal transcapillary water flux in chronic extrahepatic portal hypertension (portal venous pressure = 21.4 ± 2 mm Hg; mean ± SEM), increased 5-fold (93 ± 12 from 17 ± 4 μl/min/kg, \( P < 0.001 \)), while intestinal total protein flux expressed as protein clearance (intestinal transcapillary water flux \( \times \) intestinal lymph/plasma total protein concentration) was unchanged (13 ± 3 from 10 ± 2 μl/min per kg; \( P > 0.4 \)), a finding supported by unaltered whole body plasma albumin "leak rate" (83 ± 16 from 80 ± 2 μl/min per kg; \( P > 0.9 \)). In acute portal vein constriction (portal venous pressure = 26 ± 1 mm Hg) intestinal transcapillary water flux was similarly increased (58 ± 16 from 9 ± 2; \( P < 0.014 \)) but intestinal total protein flux was increased 3-fold (16 ± 4 from 5 ± 2; \( P < 0.032 \)). Calculated permeability surface area product and protein reflection coefficient (cross-point method) increased similarly in both preparations. In accord with earlier findings in patients with hepatic cirrhosis, chronic elevation in portal pressure increased intestinal transcapillary water flux but not total protein flux. (Circ Res 53: 622-629, 1983)

WHEREAS Starling's hypothesis is known to govern transcapillary movement of water, factors regulating transport of larger molecules are more complicated. Some evidence tends to favor transport of protein in proportion to bulk flow of water (i.e., filtration or convection) (Lassen et al., 1974). Other findings support a dissipative process, such as diffusion, independent of capillary pressure and determined by the transcapillary concentration gradient (Chinard et al., 1955; Szabo, 1976), or, alternatively, transendothelial migration through pinocytotic vesicles (Bruns and Palade, 1968; Shea et al., 1969). Whereas Krogh et al. (1932), Shirley et al. (1957), and Fishman and Pietra (1978) propose that increased hydrostatic pressure "stretches" capillary pores, thereby increasing bulk leakage of protein, Studer et al. (1973) and Brigham and Owen (1977) report continued or even greater restriction to macromolecular transport until inordinately high pressure actually ruptures capillaries.

Current understanding of transcapillary protein transport in the splanchnic bed, especially in disease states, is also incompletely understood. In patients with hepatic cirrhosis, impaired transhepatic portal blood flow promotes a substantial rise in portal pressure within both the liver and digestive tract. Portal congestion ensues, along with a considerable rise in visceral capillary filtration, as reflected by excess formation of thoracic duct lymph. When augmented lymph absorption fails to keep pace with accelerated formation, ascitic fluid accumulates (Witte et al., 1980). Earlier, we examined hepatic and extrahepatic (splanchnic) transcapillary water and protein movement by sampling visceral and thoracic duct (central) lymph in patients with hepatic cirrhosis undergoing laparotomy primarily for management of varix hemorrhage, with or without concomitant ascites (Witte et al., 1981). Although clearance of protein from plasma into central lymph was increased, the extrahepatic splanchnic protein contribution (in contradistinction to the cirrhotic liver component) was unchanged, despite a 3-fold rise in water flux. These findings not only implied a change in capillary permeability (Katz, 1983), but also suggested the importance of a dissipative (nonconvective) process, such as diffusion or vesicular transport, in protein movement across hypertensive intestinal capillaries.

To explore this phenomenon further, we now report protein clearance into regional and central lymph in dogs with chronic (C-EHPH) as compared with acute extrahepatic portal hypertension (A-EHPH). These preparations minimized the influence of liver congestion and the contribution of hepatic lymph to thoracic duct lymph flow and protein composition (complicating the picture in patients...
with cirrhosis), while allowing comparison of lymph protein transport in short-term and longer term experiments simulating chronically ill patients.

Methods

After dogs had been without food but with water ad libitum for 24 hours, operative procedures and manipulations were carried out under sodium pentobarbital anesthesia (25 mg/kg) supplemented with 50 mg every 30–45 minutes. Ventilation was controlled by endotracheal intubation and a Harvard animal respirator. In each dog, before the abdomen had been opened in C-EHPH and, afterward, in A-EHPH, the thoracic duct was cannulated in the left neck, and central lymph flow rate was determined by gravity drainage (tip of cannula at level of heart approximately 5–7 cm below thoracic duct-venous junction) at 10-minute intervals. Portal venous pressure was measured by saline manometry or strain-gauge transducer and recorder via a catheter inserted into a jejunal venous tributary. Arterial pressure was monitored continuously by transducer from an indwelling femoral arterial catheter. Regional lymph was sampled with fine needles and microhematocrit tubes from lymphatics in the liver hilum and from small lymph channels within the intestinal mesentery. Total protein content was determined in lymph and plasma by refractometry (American Optical T/S meter).

Chronic Extrahepatic Portal Hypertension (C-EHPH)

In 14 dogs (13 mongrel and one greyhound) (weight 12–27 kg) an aorto-portal shunt was constructed between the abdominal aorta (either at the level of the diaphragm above the celiac axis in three dogs or below the renal arteries in 11 dogs) and the mid-portal vein, using a reversed segment of autologous external jugular vein. The proximal (hepatic side) portal vein was progressively narrowed at the liver hilum either by concomitant placement of an ameroid (casein hydrolysate) constrictor (nine dogs) or by staged laparotomy with gradual tightening of a portal venous ligature (five dogs) (Fig. 1). Fifteen other dogs were similarly prepared, but 10 died within 24 hours from intense splanchnic venous pooling, and five died 3–4 days later from hemorrhagic shock after spontaneous disruption of the aortic suture line.

Two to 10 days after induction of splanchnic venous hypertension, final studies were carried out (see above). Additionally, in eight of these dogs before further surgical manipulation and in five nonoperated dogs (control), 10 mCi of radioiodinated human serum albumin (131I, E.R. Squibb) were administered into a central vein, arterial blood was sampled seven times over 1 hour, and aliquots of plasma were counted for radioactivity in a well-type scintillation counter (Nuclear-Chicago). Plasma volume (ratio of radioactivity of injected radiolabeled albumin:radioactivity of plasma sample at 5 minutes), intravascular mass of albumin (IVM) (product of plasma volume and plasma albumin concentration), transvascular escape rate (TER) of albumin (monoexponential fit using least squares method of disappearance over 60 minutes), and plasma albumin "leak rate" (µl/min per kg) (TER × IVM) were calculated according to the method of Henrikse et al. (1981).

Acute Extrahepatic Portal Hypertension (A-EHPH)

In eight mongrel dogs (15–29 kg) after mesenteric and liver lymph had been sampled, resting portal pressure was measured and a fine-adjustable screw-clamp placed around the portal vein high in the porta hepatitis. The thoracic duct then was cannulated and central lymph flow measured for three 10-minute periods (control). The screw-clamp was then gradually tightened to raise portal pressure to 25 mm Hg from approximately 8 mm Hg, and thoracic duct lymph flow and total protein content of TDL and plasma were serially determined during the next 2 hours. Thereafter, the abdomen was reopened and mesenteric and liver lymph resampled. In five dogs, measurements continued after unclamping the portal vein for 2 more hours.

Data were transferred to keypunch cards, entered on a DEC 20 computer for calculations, and statistical analysis carried out using a statistical package for the social sciences (SPSS). Differences were analyzed by paired and non-paired Student's t-test where appropriate. Measurements were expressed as mean ± SEM. Descriptors of capillary permeability were computed on an HP-85 computer using a "cross-point" program devised by M.A.K. (Brace et al., 1978).

Calculations and Rationale

Intestinal and Hepatic Lymph Flow and Protein Transport

Based on the assumption that, at rest, the bulk of thoracic duct lymph originates from the digestive tract and liver, a previously described "mixture formula" was used to quantify the relative contributions of splanchnic and hepatic lymph to thoracic duct lymph (Witte et al., 1981). Briefly, net transcapillary water (volume) flux (J,)
was equated with measured and calculated lymph flow rates \((J_L, J_L')\), and transcapillary protein transport \((J_P)\) was calculated from the product of \(J_L\) and lymph protein concentration \((C_L)\). Because thoracic duct lymph flow \((TDL)\) derives largely from liver lymph \((LL)\) and intestinal lymph \((IL)\) \(\text{(Morris, 1956)}\), i.e., \(J_{IL} + J_{LL} = J_{TDL}\) and \(J_{IL} + J_{LL} = J_T\), and \(C_{TDL} C_{LL} C_{IL}\) were measured, intestinal lymph flow \((J_{IL})\) was calculated as:

\[
J_{IL} = J_{TDL} \left( \frac{C_{TDL} - C_{LL}}{C_{IL} - C_{LL}} \right).
\]

Because of differences in plasma protein concentration, the data were standardized by converting total protein transport to plasma clearance \(\text{(i.e., the volume of plasma cleared of protein per minute into TDL and IL)}\) by dividing the respective \(J_P\) values by the measured plasma protein concentration \((C_P)\). From these measured and derived values, net transcapillary water and total protein flux were determined in the intestine. Evidence for the dual origin of TDL from the liver and intestine has been detailed previously \(\text{(Witte et al., 1981)}\). Some workers \(\text{(Pinter et al., 1967; Mayerson et al., 1958; Mcintosh and Morris, 1971; Peterson et al., 1975; Brace et al., 1978; Katz, 1980)}\) fail to corroborate this assertion. Moreover, isolated extrahepatic portal hypertension would not be expected to raise renal lymph production. Accordingly, the kidney is disregarded as a contributor to thoracic duct lymph flow in these experiments.

\(\sigma, PS, \text{ and Diffusive-Convective Fluxes by Kedem-Katchalsky Cross-point Method}\)

Because net transcapillary protein flux \((J_P)\) equals the sum of convective and nonconvective or diffusive flux, and because excess capillary filtrate containing protein eventually circulates back to the bloodstream as lymph, we estimated the contribution of these two processes to protein transport by measuring lymphatic fluxes based on the Kedem-Katchalsky \((K-K)\) equation \(\text{(Kedem and Katchalsky, 1958)}:\)

\[
J_P = J_V (1 - \sigma) C_L + PS (C_P - C_L)
\]

where \(J_V\) is volume flux or lymph flow; \(C_L\) the mean transmembrane solute concentration; \(P\) the solute permeability of the capillary membrane; \(S\) the membrane surface area; \((C_P - C_L)\) the protein concentration difference between plasma \((C_P)\) and lymph \((C_L)\); \(\sigma\) the reflection coefficient; and \(PS (C_P - C_L)\) the diffusive and \(J_V (1 - \sigma) C_L\) the convective component of protein transport.

To determine \(\sigma\) and \(PS\), we used the cross-point method, taking advantage of an isomorphic transformation of the updated K-K equation into the form \(\text{(Chang et al., 1975; Brace et al., 1978; Katz, 1980)}:\)

\[
PS = \frac{J_V (1 - \sigma) C_L}{\ln \left( \frac{R_S}{R - (1 - \sigma)} \right)}
\]

where \(R_S\) is the lymph:plasma protein ratio or \(C_P: C_L\). This formulation does not assume the nature of \(C_L\), but only that the K-K equation can be written at a point across the membrane and that this function is integrable.

For any two data points \(\text{(i.e., } J_{IL}, R_1\text{, and } J_{IL}, R_2)\) two sets of Equation 3 were formulated and solved for \(\sigma\) and \(PS\) values comparable for both data sets of Equation 3 were formulated and solved for \(\sigma\) and \(PS\), we used the cross-point method, taking advantage of an isomorphic transformation of the updated K-K equation into the form \(\text{(Chang et al., 1975; Brace et al., 1978; Katz, 1980)}:\)

Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>PVP (mm Hg)</th>
<th>TDLQ (nl/min per kg)</th>
<th>Total protein (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TDL</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>C-EHPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32</td>
<td>94</td>
<td>13</td>
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<tr>
<td>2</td>
<td>22</td>
<td>125</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>231</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>75</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
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<td>120</td>
<td>9</td>
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<tr>
<td>6</td>
<td>32</td>
<td>169</td>
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<td>7</td>
<td>25</td>
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<td>55</td>
<td>14</td>
</tr>
<tr>
<td>Mean</td>
<td>21</td>
<td>196</td>
<td>14</td>
</tr>
<tr>
<td>SEM</td>
<td>2</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>SEM</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(PVP = \text{portal venous pressure; TDLQ = thoracic duct lymph flow; TDL = total protein in thoracic duct; IL = intestinal lymph; LL = hepatic lymph; A = ascitic fluid; P = plasma; C-EHPH = chronic extrahepatic portal hypertension.}\)
Table 1 summarizes direct measurements in dogs with C-EHPH and controls. Thoracic duct lymph flow increased 5-fold (P < 0.001) while the protein concentration in thoracic duct and intestinal lymph fell proportionately. Despite a 6-fold increase in calculated intestinal lymph flow (water flux) (93 ± 12 from 17 ± 4 μl/min per kg; P < 0.001), protein clearance (flux) was unchanged (13 ± 3 from 10 ± 2 μl/min per kg; P > 0.4) (Fig. 2). When intestinal lymph:plasma (L:P) protein ratio was plotted against portal pressure, a sharp decrease was seen with low level portal hypertension and a smaller further decline at higher portal pressure levels (Fig. 3).

Based on regional and central lymph protein concentrations, measured TDL flow was highly correlated (r = 0.98) with calculated IL flow, signifying that excess TDL derived from the intestine. Whereas IL water flux increased proportionately as portal pressure rose (r = 0.78, P < 0.001), intestinal protein clearance was unchanged over a wide range of portal pressures (r = 0.02, P > 0.4) (Fig. 4) and was unrelated to water flux (r = 0.28, P > 0.1) (Fig. 5). Furthermore, whole body albumin leak rate (83 ± 16 from 80 ± 2 μl/min per kg, P > 0.9) was unaltered by increased portal pressure (r = —0.27, P > 0.22).

In eight of these dogs, ascitic fluid accumulated in moderate amounts (50–500 ml). Except for appearing slightly blood-tinged, the ascitic fluid was thin and watery, and the protein content was low (10 ± 2 mg/ml). The extrahepatic portal bed in the dogs with portal pressure > 20 mm Hg was intensely congested with thickened edematous small bowel and distended mesenteric lymphatics from which fluid flowed rapidly after pricking. In addition, portasystemic collaterals were abundant while the liver and its lymphatic network cephalad to the portal vein constrictor appeared normal.

Figure 6 displays serial changes in arterial and portal venous pressure, TDL and plasma protein content, and TDL:P protein ratio, before (control), during, and after release of portal vein constriction. After 2 hours of elevated portal pressure, TDL flow

\[ \text{Intestine} \]
\[ \text{Clearance (μl/min/kg)} \]
\[ \text{Water} \]
\[ \text{Protein} \]

**Figure 2.** Estimated net transcapillary clearance of water and total protein into intestinal lymph in 14 dogs with extrahepatic portal hypertension. The cross-hatched area represents the 95% confidence limits for control values in five dogs and solid horizontal bar the mean values in the experimental group. In calculation of water clearance, it was assumed that the concentration of water in plasma and lymph was identical.

**Figure 3.** Intestinal lymph:plasma protein ratio (R) vs. portal pressure showing the steep decline in intestinal R with low level portal pressure elevation. Solid squares represent control dogs, whereas solid circles are experimental values.

**Figure 4.** Comparison of response of net intestinal transcapillary water and protein clearance to elevation in portal pressure in dogs with chronic extrahepatic portal hypertension. Despite a sizable increase in transcapillary water movement, protein clearance into intestinal lymph was unchanged. In determination of water clearance it was assumed that the concentration of water in lymph and plasma was identical.
was increased 5-fold (63 ± 10 from 14 ± 2 µl/min per kg, P < 0.003), whereas TDL and IL protein concentration decreased to 23 ± 3 and 20 ± 4 mg/ml from 44 ± 1 and 39 ± 2, respectively (P < 0.001). Liver lymph protein content (53 ± 2 from 50 ± 2 mg/ml; P > 0.17) was unchanged. Calculated intestinal water flux increased 6-fold from 9 ± 2 to 58 ± 13 µl/min per kg (P < 0.014), while IL:P ratio was halved (0.62 ± 0.02 to 0.30 ± 0.05 P < 0.003), resulting in a 3-fold increase in protein clearance (5 ± 2 to 16 ± 4 µl/min per kg; P < 0.032). In contrast to C-EHPH, intestinal protein flux during A-EHPH correlated directly with water flux (r = 0.78). Within 2 hours after release of the constriction, all measurements and calculations had returned to or closely approached control values.

Table 2 summarizes estimated σ and PS derived from the cross-point method, along with calculated absolute and fractional diffusive protein transport in control, A-EHPH, and C-EHPH dogs. As expected, because of intrinsic errors in J and R, only a minority of possible data pairs actually crossed. Although some consider this discrepancy an indication of membrane heteroporosity (Blake and Staub, 1976; Taylor et al., 1977; Brigham et al., 1979), others suggest that heteroporosity alone is insufficient to account for limited numbers of crossing pairs of data (Winn et al., 1981), and still others propose that the capillary membrane itself becomes more restrictive as pressure rises (Katz, 1980). For C-EHPH, there were nine theoretical and 50 possible cross-points, of which only 11 yielded results compared with the control of 10, 3, and 2, respectively. For A-EHPH, there were 28 theoretical and 16 possible cross-points, of which 11 yielded results compared with control of 28, 18, and 11, respectively. These data revealed a sharp rise in σ and PS, as well as in absolute and fractional diffusive transport. Whereas fractional convective transport decreased in both, absolute convective transport increased only in A-EHPH.

**Discussion**

Transcapillary movement of protein from plasma into lymph has previously been examined in acute venous hypertension during volume expansion in the whole animal (Mayerson, 1963) and in partially isolated organ systems (Garlick and Renkin, 1970, Granger et al., 1979). As in the present study of dogs with acute extrahepatic portal hypertension (A-EHPH), while tissue protein washdown occurs, total

**Table 2**

### Cross-point Method Determination of Reflection Coefficient, Permeability-Surface Area Product, and Diffusive Component* of Transcapillary Total Protein Clearance in Experimental (A-EHPH and C-EHPH) and Control Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>A-EHPH</th>
<th>Control</th>
<th>A-EHPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>σ (µl/min per kg)</td>
<td>0.47 ± 0.4</td>
<td>0.80 ± 0.02</td>
<td>0.45 (0.37,0.53)</td>
<td>0.86 ± 0.02</td>
</tr>
<tr>
<td>PS (µl/min per kg)</td>
<td>5.2 ± 0.9</td>
<td>5.4 ± 2.0</td>
<td>3.6 (4.2,2.9)</td>
<td>8.3 ± 1.7</td>
</tr>
<tr>
<td>Diffusive component</td>
<td>1.3 ± 0.4</td>
<td>6.2 ± 1.6</td>
<td>1.4 (1.5,1.3)</td>
<td>6.5 ± 1.2</td>
</tr>
<tr>
<td>Absolute (µl/min per kg)</td>
<td>22 ± 6</td>
<td>40 ± 7</td>
<td>19 (11,27)</td>
<td>43 ± 6</td>
</tr>
</tbody>
</table>

*Results are expressed as mean ± se. σ = reflection coefficient; PS = permeability-surface area product; A-EHPH and C-EHPH = acute and chronic extrahepatic portal hypertension.

* Absolute and fractional.
protein transport in lymph nonetheless rises, suggesting that at least a portion (about one-half) of macromolecular flux is by convection. Short-term experiments, however, assume that equilibration of protein concentration takes place rapidly. Yet acute elevations in venous pressure are accompanied by suddenly shifting vascular wall compliance, autoregulation, and veno-arteriolar responses (Johnson and Richardson, 1974), while washout of extant tissue protein may be incomplete. Aukland and Nicolaysen (1981), after an exhaustive review of tissue regulatory forces, conclude that it is highly unlikely that the interstitium attains steady state protein concentration gradients in just a few hours after sudden alterations in filtration rate or capillary permeability, whereas Engeset et al. (1979) have shown that it takes more than 24 hours for intravenously administered radiiodinated albumin to equilibrate in peripheral lymph of active patients. Another equilibrium problem is temporary exclusion of macromolecules in the interstitium due to collagen, mucopolysaccharides, or other structural components. Thus, with acute venous pressure elevation, coexistent alterations in interstitial compliance and matrix may account for some tissue fluid-lymph protein washout without de novo change in plasma protein leakage. Time-dependent alterations in interstitial compliance from "stress relaxation," i.e., tissue stretching with delayed readjustment in compliance, also exert unpredictable effects on washout and dilution during acute manipulation. It is probably unwarranted, therefore, to assume a well-mixed interstitium after acute perturbations. Despite these considerations, computed $\sigma$, PS, diffusive transport, and fractional diffusive transport (as calculated from the limited number of successful dog pairings exhibiting crosspoints) were virtually the same in acute and chronic studies (Table 2).

The "chronic" experiments were designed to simulate intense extrahepatic portal congestion characteristic of patients with hepatic cirrhosis. Because experimental obstruction to the portal vein alone, even in stages, fails to sustain portal pressure elevation comparable to the clinical syndrome (Witte et al., 1978), we combined hyperdynamic arterial flow (aortic-portal venous fistula) with portal vein constriction, a maneuver previously shown to induce marked and sustained portal hypertension (Tamia and Thal, 1960; Witte et al., 1969). Although only eight dogs developed portal pressures greater than 20 mm Hg, the wide variation provided an unusual opportunity to examine transcapillary fluxes over a larger range of portal pressure in a reasonably stable preparation.

The data in C-EHPH support the findings in patients with hepatic cirrhosis that macromolecular movement in the intestinal microcirculation is not enhanced during portal hypertension and, further, is largely uninfluenced by the increased movement of water (i.e., solvent drag). The greatest dilution of tissue fluid (lymph) protein takes place after a relatively small increment in portal pressure. The widened transcapillary colloid osmotic pressure gradient then acts as a potent safety factor against progressive edema (Mortillaro and Taylor, 1976).

The main difference between A-EHPH and C-EHPH lies not in membrane permeability changes but in the degree of tissue protein washdown. Thus, whereas increases in water flux were proportionately similar (i.e., lymph flow rose 5- to 6-fold), lymph protein washdown was much greater in long-than in short-term experiments, indicating a steady state for water flux within 2 hours after venous pressure elevation, but considerably later for protein equilibration.

When data in eight dogs with C-EHPH in excess of 20 mm Hg were examined separately, findings were remarkably close to those in patients with cirrhosis, where splanchnic venous pressure averaged 25 mm Hg (Witte et al., 1981). Specifically, thoracic duct lymph flow increased 6-fold, lymph protein content in central and mesenteric lymph were 17% and 10% of plasma, respectively, and calculated solute flux (expressed as protein clearance into lymph) was normal, despite markedly increased water flux. In contrast to patients with cirrhosis, however, where intense intrahepatic as well as extrahepatic portal hypertension contributes to excess thoracic duct lymph and apparently accounts for an overall increase in protein flux (Witte et al., 1981), C-EHPH dogs had nearly pure extrahepatic portal congestion. This difference probably accounts for their lower TDL:P protein ratio (17%) compared with patients (32%), where the hypertensive cirrhotic liver contributes substantially to increased TDL protein content (Witte et al., 1981). Increased hepatic lymph production of borderline significance was also observed, despite lack of gross and microscopic hepatic congestion. Most likely, when the amoroid constrictor failed to restrict transhepatic portal flow sharply (i.e., dogs with portal venous hypertension < 20 mm Hg), increased blood flow reached the sinusoid through the aortic-portal shunt. Without impedance to hepatic venous outflow, however, sinusoidal pressure elevation from hyperdynamic portal flow is usually small (Witte et al., 1978), probably accounting for the slightly increased hepatic transcapillary water and protein flux.

Unaltered whole body albumin leak from the plasma compartment (calculated from disappearance of radiiodinated albumin) and lack of correlation with portal pressure level in C-EHPH further support the conclusion that intestinal protein flux is not increased during sustained portal hypertension. Although our control leak rates in dogs are considerably higher than those reported by Parving et al. (1977) in man, the values are comparable to other reports (Wasserman and Mayerson, 1951; Huggins et al., 1963) in dogs, and are less than recently reported by Henriksen et al. (1981) in pigs.

Analysis of shifting capillary surface exchange...
area and permeability during portal pressure elevation is complex. Nonetheless, for animals yielding cross-points, estimated diffusive fraction rose 2- to 4-fold with increased protein concentration gradient and doubled PS product, whereas fractional convective transport was reduced with rising $\sigma$ and decreased mean relative membrane protein concentration $(C/C_p)$. These findings are not only inconsistent with the "stretched pore" concept, but also suggest that pores, if present, narrow with increased pressure (Chen et al., 1976; Brigham et al., 1979; Zweifach, 1980; Katz, 1981), and that more narrow pores are present after capillary pressure elevation than before. Shift from convective to diffusive protein transfer may be due to distributional changes in blood flow with enlarged surface area (Brigham et al., 1979), flattening of endothelial cells with increased tortuosity of interendothelial cell junctions (Zweifach, 1980), or greater elliptical eccentricity of pores with a net decrease in effective radius. Alternatively, current methods to estimate PS and $\sigma$ may simply be inadequate because of incorrect assumptions in the mathematical formulation.

Thus, in dogs with C-EHPh, where sufficient time is allowed for equilibration of tissue protein dilution, neither total protein flux, as determined by plasma protein clearance into intestinal lymph, nor whole body albumin leak from the plasma space, supports increased egress of macromolecules from intestinal capillaries despite a large outpouring of fluid. These findings, along with a rise in PS and $\sigma$, suggest that filtration or convection contributes less and diffusion or vesicular transport more to protein transport in the intestinal microcirculation as portal pressure rises.

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