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Lymph Protein in Hepatic Cirrhosis and Experimental Hepatic and Portal Venous Hypertension

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DURING investigations into the influence of mechanical factors on lymph production, Starling [43] demonstrated that pre- and posthepatic venous obstruction produced characteristic changes in the protein content of thoracic duct lymph (TDL). He observed that after supradiaphragmatic inferior vena cava constriction, TDL of increased protein content was derived predominantly from high-protein liver lymph (LL), whereas after portal vein ligation, TDL of lowered protein content originated primarily from low-protein intestinal capillary filtrate.

In patients with cirrhosis of the liver portal inflow and hepatic outflow venous obstruction may coexist [31] and are accompanied by increased flow of TDL.[12, 13] Exact origin of excess TDL is unclear, however, as is the relationship between ascites formation and the site of venous obstruction. The fact that lymph originating in the liver can be distinguished from lymph formed in the extrahepatic portal bed by its uniquely high protein content was used in this study to determine the relative influence of pre and postsinusoidal obstruction on the production of TDL and ascitic fluid in hepatic cirrhosis. Protein content of TDL, LL, intestinal lymph (IL), ascitic fluid and plasma was measured in various combinations in 68 patients with cirrhosis, including 10 after portacaval shunt. These results were compared with findings in control subjects and in experimental animals with hepatic and portal venous hypertension.

Methods

A. Experiments on Dogs

Twenty-one healthy mongrel dogs (10–15 Kg.) were studied. General anesthesia was induced with intravenous Myotal (0.3 ml./Kg.) and breathing controlled by positive pressure respiration at constant rate and volume. When samples of lymph were

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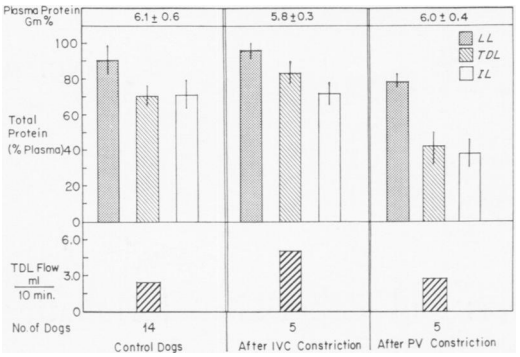


FIG. 1. Total protein in thoracic duct, liver and intestinal lymph (mean ± SD) in dog after acute constriction of thoracic inferior vena cava (IVC) or portal vein (PV). Corresponding thoracic duct lymph mean flow rate is shown.

drawn for analysis, skeletal muscular activity was abolished by succinyl choline (0.1 mg./Kg.). The portal vein, abdominal vena cava and aorta were cannulated and arterial, cava and portal pressures recorded either continuously using pressure transducers and a multichannel direct writing polygraph (Sanborn) or intermittently with saline manometry (venous pressure only). The thoracic duct was cannulated in the right chest and lymph allowed to drain by gravity through an indwelling polyethylene catheter.

Flow rate was recorded at 10-minute intervals and essentially all lymph collected was returned intravenously. Administration of other fluids was limited to catheter irrigation or manometric measurements and never exceeded 50 cc. of saline in any one experiment. Liver lymph was obtained from a periportal hilar lymphatic and intestinal lymph from a lymphatic channel which regularly paralleled the inferior border of the superior mesenteric artery. Total protein content of LL, IL (regional lymph) and TDL, plasma and ascitic fluid (if present) was measured using a T/S refractometer (Model 10401 American Optical) requiring approximately one drop of fluid. Three groups of animals were studied.

Group I (five dogs). In three dogs after a control period of 1 hour, the thoracic inferior vena cava (IVC) was constricted approximately 50% by silk ligature and serial changes in LL, IL, and TDL determined for 60 minutes. In two other dogs LL and IL were not sampled until 60 minutes after cava constriction to avoid the effects of interrupting these pathways on TDL.

Group II-a. In five dogs a protocol similar to group I was followed except the portal vein (not the IVC) was narrowed to raise mesenteric venous pressure 2.5 to 3 times control value without markedly altering arterial pressure.

Group II-b. In two dogs the portal vein was narrowed by silk ligature approximately 50% to raise mesenteric venous pressure between 19–22 cm. saline, and 1–2 weeks later the animals were restudied. After control specimens were determined for 1 hour the portal vein was completely ligated and serials samples continued for another 60 minutes.

Control values for LL, IL, TDL and plasma were determined in 14 dogs including those in group I and II-a prior to venous obstruction.

Group III (five dogs). The thoracic inferior vena cava was constricted approximately ⅓ of its external diameter with umbilical tape and 1–2 weeks later the dogs were restudied. Ascitic fluid, regional and thoracic duct lymph protein and TDL flow were determined, and the portal vein then constricted as in group II-a.

B. Clinical Observations

The thoracic duct was cannulated in the neck with polyethylene tubing under local anesthesia. Flow rate by gravity drainage and protein content was measured in 68 patients with hepatic cirrhosis and in 13 control subjects (2 normal volunteers, 8 with calculous biliary tract disease without evidence of hepatic cirrhosis, and 3 with localized abdominal malignancy). Ages ranged from 25–75 years with the majority in the fourth and fifth decade. Portal pressure was determined by splenic puncture, umbilical vein catheterization or by cannulation of an omental or mesenteric vein during laparotomy in 44 patients.. Liver lymph from periportal or hepatic capsular

lymphatics and IL from mesenteric lacteals were obtained during laparotomy in 11 patients including eight with cirrhosis and three control subjects (two during simple cholecystectomy and one during resection of a localized esophageal carcinosarcoma). Ascitic fluid was obtained during laparotomy or via abdominal paracentesis in 28 patients with cirrhosis. In four patients flow rate and protein content of TDL was determined within 24 hours after portacaval shunt operation and in another six patients at varying subsequent intervals ranging from 2–4 weeks. Protein content in ascitic fluid, lymph and plasma was measured by salt fractionation (Biuret method) [19] or with a T/S refractometer.

Results

Figure 1 summarizes the effects of acute portal and vena cava obstruction in dogs on total protein levels in LL, IL and TDL expressed as per cent of plasma content. Control values of LL, IL and TDL protein were similar to previous reports [18, 20] and remained unaltered during a 60-minute observation period.

Group I—Within 20 minutes after constriction of the supradiaphragmatic inferior vena cava both flow rate and protein content of TDL regularly increased. Concentration of protein in LL, if not already near plasma level, also increased, but IL concentration was unchanged (Fig. 2).

Group II-a—Acute portal vein constriction produced a rapid fall in intestinal and TDL protein levels. Although TDL flow rates varied, the mean was unchanged. Intestinal lymph flowed profusely after portal vein constriction, but liver lymphatics collapsed and LL protein diminished slightly (Fig. 3a). In two dogs with undisturbed regional lymphatic pathways, TDL flow increased in one and did not change in the other. Figure 4 summarizes the results of prolonged hepatic venous inflow and outflow obstruction on regional and TDL protein and TDL flow.

Group II-b—Two-staged portal vein occlusion resulted in more prolonged mesenteric congestion and a marked decrease in IL and TDL protein (Fig. 3b). Concentrations in liver lymph, normally 90% of plasma level, decreased to 73% of plasma ($p < 0.001$). Mean TDL flow remained at control values. Neither animal developed ascites and prior to secondary complete ligation portal pressure had returned to less than 16 cm. of saline.

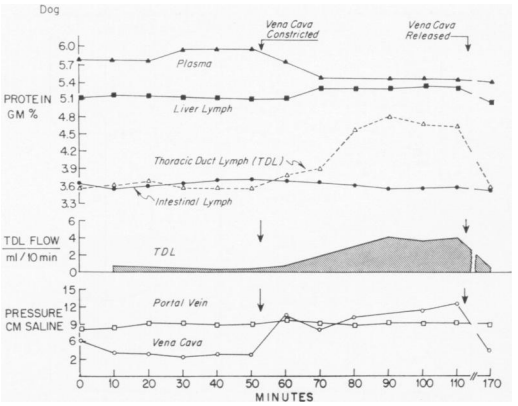


FIG. 2. Characteristic effect on thoracic duct (TDL), liver, intestinal lymph, and plasma protein, and thoracic duct lymph flow rate in dog after acute constriction of the thoracic inferior vena cava.

Group III—Ascitic fluid developed in each dog with chronic caval constriction and this fluid contained high concentration of protein (61% ± 5). Portal pressure was elevated in only one at time of restudy (18 cm. saline). The thoracic duct and hepatic lymphatics were enormously distended and flow from the thoracic duct was markedly increased. At times both ascitic fluid and periportal lymph appeared hemorrhagic. Plasma protein levels were slightly below control animals but LL, IL and TDL protein (as % plasma) were close to control values. As portal pressure increased following portal vein ligation, TDL and IL protein content rapidly decreased to levels resembling those observed in chronic portal constriction (Figs. 4, 5). Increased TDL flow rate was not altered by portal vein constriction, but again IL appeared to flow vigorously and LL became less readily accessible.

Figures 6–8 summarize data from human subjects. In control subjects LL, IL and

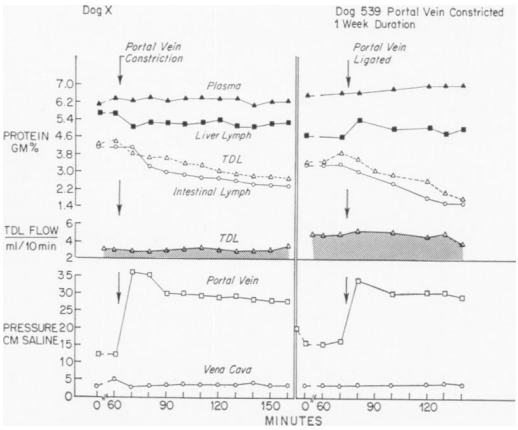


FIG. 3. a) Left—Characteristic effect on thoracic duct, liver, intestinal lymph and plasma protein, and thoracic duct lymph flow rate in dog after acute constriction of the portal vein. b) Right—More pronounced decrease in thoracic duct and intestinal lymph protein after two-stage portal vein ligation.

TDL protein levels were similar to values observed in normal dogs. Flow rate from the thoracic duct averaged 0.8 ml./min. (range 0.5–1.8 ml./min.).

In 19 patients with hepatic cirrhosis with no history of bleeding esophageal varices who presented in a less advanced stage of the disease, TDL flow was elevated (5.4 ml./min.), and protein content was either normal or high (mean = 71%). Ascitic fluid samples in this group had a high protein content (45%). In one patient LL and IL protein were also high (81%). In 10 other patients with moderately advanced cirrhosis usually presenting with jaundice as well as ascites but without bleeding esophageal varices, TDL protein was 50% and ascitic fluid protein 18%. In 41 additional patients who were in the "late" stages of the disease with marked portal hypertension (37 cm. saline) and severely deranged liver function, and who manifested bleeding esophageal varices, mean TDL protein was low (32%) and fell even lower (15%) when portal blood flow was blocked by cross-clamping the portal vein prior to portacaval anastomosis.

Flow rate from the thoracic duct was uniformly elevated (not significantly different from "early" cirrhosis, $p > 0.1$) until a portacaval shunt was established after which it returned to normal or near normal levels. Intestinal and LL protein content were low with the former only 1/9 the normal value. Ascitic fluid protein in this group averaged only 13% and approximated the protein value for IL (8%). After portacaval shunt and reduction in portal pressure, TDL protein increased to 47% of plasma level and flow diminished to 2 ml./min. One patient temporarily accumulated ascitic fluid after operation with protein content of 48%. In another patient with malfunction of the shunt (portal pressure fell slightly from 46 cm. to 43 cm.) ascitic fluid containing small amounts of protein (8%) developed postoperatively at rapid rate until death ensued on the tenth postoperative day.

In four patients with cirrhosis plus portal vein occlusion, including two with portacaval shunt thrombosis, TDL, IL, LL and ascitic fluid protein averaged only 19%, 1%, 27% and 2%, respectively, of plasma content.

Detailed analysis of thoracic duct lymph flow, end pressure, and sulfobromophthalein (BSP) content in these patients will be reported separately.[49]

Discussion

Ludwig was the first to propose, in 1861, that lymph originates from plasma by capillary filtration regulated by intravascular pressure.[28] Later, Starling [44] and then Landis [26, 27] emphasized that lymph formation is controlled by a balance of forces including hydrostatic pressure on both sides of the capillary membrane, colloid-osmotic pressure of plasma and tissue fluid, and permeability of the capillary wall. Arterial pressure initiates capillary filtration but hydrostatic pressure in the venous limb of the capillary is lower than colloid-osmotic pressure of plasma protein, and protein-free interstitial fluid is partially reabsorbed. Protein which has leaked into the interstitial space and excess tissue fluid eventually return to the blood stream through lymphatic channels. Accordingly, changes in lymph

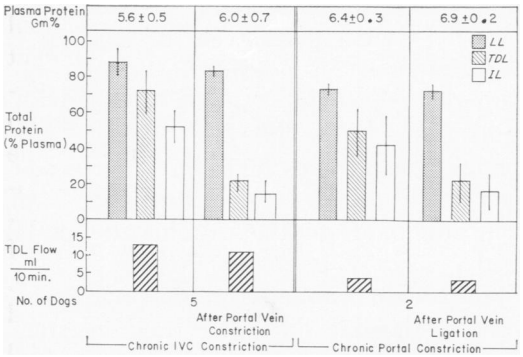


FIG. 4. Total protein in thoracic duct, liver and intestinal lymph (mean ± SD) in dog after chronic constriction of the thoracic inferior vena cava (IVC) or portal vein followed by acute portal vein obstruction. Corresponding thoracic duct lymph mean flow rate is shown.

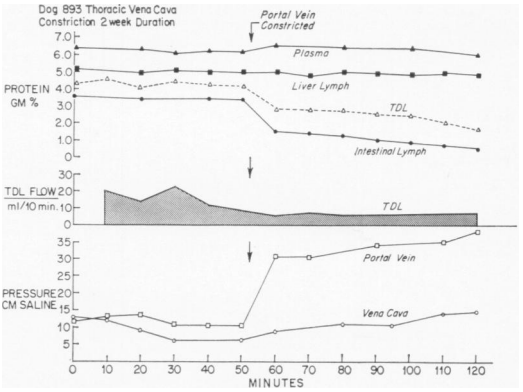


FIG. 5. Characteristic effect on thoracic duct (TDL), liver, intestinal lymph and plasma protein, and thoracic duct lymph flow rate in dog after chronic caval and acute portal vein constriction.

flow and protein concentration reflect alterations in capillary filtration or net production of tissue fluid.

Intracapillary pressure (Pc) depends on various factors including the mean capillary, arterial (Pa) and venous pressure (Pv) and the precapillary (Ra) and postcapillary (Rv) flow resistances or

$$Pc = \frac{Pa(Rv/Ra) + Pv}{1 + (Rv/Ra)}.$$ [38]

A rise in arterial pressure generally has a minimal effect on mean capillary hydrostatic pressure because of a concomitant increase in precapillary arteriolar resistance. On the other hand, a rise in venous pressure is less offset by changes in resistance, and rapidly leads to a rise in capillary pressure. This imbalance promotes a preponderance of filtration over reabsorption, accumulation of tissue fluid, and a rise in lymph flow.

Hydrostatic pressure in the liver sinusoid is derived primarily from portal vein pressure which normally does not exceed 15 mm. Hg. The hepatic artery perfuses a relatively minor portion of the liver capillary bed (the peribiliary plexus) and these capillaries terminate in a high pressure venous system.[6] The low pressure sinusoidal bed is highly permeable and allows a large amount of plasma protein to "leak" through its capillary wall.[8, 80] Effective colloid-osmotic pressure in the sinusoid, therefore, is minimized and filtration pressure is unopposed by oncotic pressure.[4] For this reason, posthepatic venous obstruction greatly increases liver capillary filtrate and liver lymph high in protein.[7, 33]

In contrast to liver sinusoids, intestinal capillaries are less permeable to plasma protein [3, 37, 47] and hydrostatic pressure is derived exclusively from arterial pressure. Following portal vein obstruction a rise in hydrostatic pressure is accompanied by greater filtration of water than of protein. The volume of IL increases but its protein concentration decreases.[25]

Excess interstitial fluid from both the small intestine and liver is transported to the thoracic duct as lymph.[32, 50] After experimental supradiaphragmatic inferior vena caval constriction a preponderance of high protein LL enters the thoracic duct. Thoracic duct lymph flow and protein content correspondingly rise. After portal vein constriction the major source of TDL is very low-protein IL, and TDL protein falls. Coincident with mesenteric venous congestion and visibly enhanced IL flow, however, hepatic lymph is obtained only with great difficulty as flow from periportal lymphatics almost ceases. A corresponding reduction in hepatic sinusoidal pressure probably accompanies the rise in mesenteric capillary hydrostatic pressure.[4] Thoracic

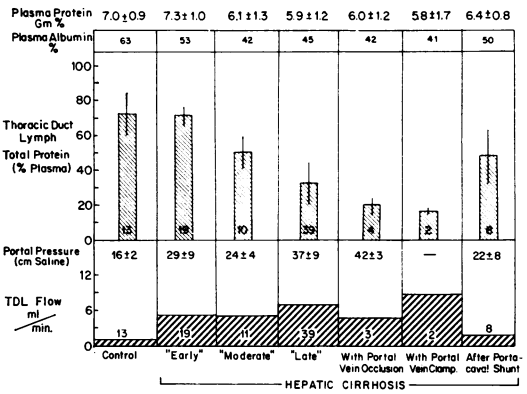


FIG. 6. Total protein in thoracic duct lymph (mean ± SD) in control subjects and in patients at different stages of hepatic cirrhosis. Mean values for thoracic duct (TDL) flow, portal pressure, plasma protein, and % albumin in plasma at comparable stages are also shown. Numbers at the bottom of each bar represent number of patients studied.

duct lymph flow depends on the sum of these effects, and the flow fluctuates depending upon the degree of venous obstruction and the relative contribution of IL and LL before and after portal vein constriction. Although this maneuver has a variable effect on TDL flow, diminution in TDL protein concentration regularly occurs.

Chronic caval obstruction greatly augments flow in the thoracic duct. In this situation, however, TDL arises not only from the liver and intestine but also from the kidneys, retroperitoneum and lower extremities. Lymph aspirated from dilated lymphatic channels in these areas had a protein content ranging from 30–45% of plasma. "Contamination" by this low-protein lymph could be averted by constriction of hepatic veins,[36] rather than inferior vena cava, and TDL would then contain an even greater proportion of LL.

These experiments confirm that hepatic venous outflow obstruction greatly increases formation of liver capillary filtrate and thereby augments TDL flow high in protein. As the transporting capacity of the hepatic lymphatic system is exceeded, high protein capillary filtrate from the liver spills into the peritoneal cavity to initiate ascites.[5, 23] When portal vein obstruction is superimposed on posthepatic venous obstruction, the bulk of excess capillary filtrate forms in the intestine. Thoracic duct lymph flow remains high, but protein concentration decreases, reflecting the large contribution from the extrahepatic portal bed.

In patients without cirrhosis, protein content of thoracic duct, liver and intestinal lymph resembles control values in dogs. In patients with cirrhosis, protein content resembles the values in animals with experimental hepatic and mesenteric venous congestion (Fig. 9a and 9b). In cirrhosis, postsinusoidal obstruction is often considered the major factor leading to increased formation of TDL and ascitic fluid.[2, 17] Presinusoidal obstruction is usually discounted as an important mechanism in the production of these fluids.

In dogs with caval or hepatic vein constriction[36] or in patients with Budd-Chiari syndrome[16, 34, 48] hepatic lymphatics are dilated and abundant, TDL flow is rapid and ascitic fluid may accumulate without marked increase in portal pressure. On the other hand, in disorders characterized predominantly by presinusoidal obstruction such as portal vein occlusion[10, 15, 42, 46] or cirrhosis due to schistosomiasis,[1, 11] ascites usually is absent or mild even if portal hypertension is pronounced.

Although posthepatic venous obstruction produces TDL and ascitic fluid of high protein content,[24] some patients with postnecrotic or nutritional cirrhosis demonstrate low protein content in both fluids (Figs. 6, 8). In these patients bleeding esophageal varices and marked portal hypertension are prominent manifestations of the disease. In contrast, patients with "less advanced" liver disease have high protein levels in ascitic fluid, LL, IL, and TDL. This difference suggests that early in cirrhosis when postsinusoidal obstruction predominates, excess LL is the major source of TDL as well as

ascitic fluid. As presinusoidal obstruction and varix bleeding develop, hepatopetal portal circulation decreases, mesenteric congestion increases, and low-protein lymph from the extrahepatic portal bed now contributes the major portion of TDL.[14] At this stage ascitic fluid probably arises from the "weeping" of excess capillary filtrate from intestinal and mesenteric serosal surfaces. The relatively low protein content of LL may signify decreased permeability or "capillarization" of the hepatic sinusoid.[39]

In extrahepatic portal venous obstruction or in cirrhosis due to schistosomiasis, liver sinusoidal perfusion and pressure is reduced by presinusoidal obstruction. Here, an increase in intestinal capillary filtration is offset by decrease in LL formation. These divergent effects of prehepatic obstruction render it unlikely that excess IL can overburden the lymphatic system. Consequently, ascites usually does not develop. Postnecrotic and nutritional cirrhosis, on the other hand, are characterized early by increased postsinusoidal resistance.[21, 22, 29, 40] Although presinusoidal obstruction and decreased portal inflow may develop later, postsinusoidal obstruction persists, excess LL continues to form, and the addition of excess IL overloads the thoracic duct. Furthermore, when the portal vein is occluded by thrombus or clamped during a portacaval anastomosis, the combination of both intrahepatic and extrahepatic portal obstruction produces the greatest mesenteric congestion and the lowest protein levels in IL and TDL. After mesenteric congestion is relieved by a portacaval shunt, TDL protein increases, reflecting a greater proportion of LL. When ascitic fluid accumulates after a successful shunt, it is high in protein and probably originates from transected hepatic lymphatics. Unless the residual postsinusoidal obstruction is severe, ascites usually disappears. In the one patient with a hemodynamically unsatisfactory shunt, ascitic fluid contained very little protein presumably because mesenteric congestion was unrelieved.

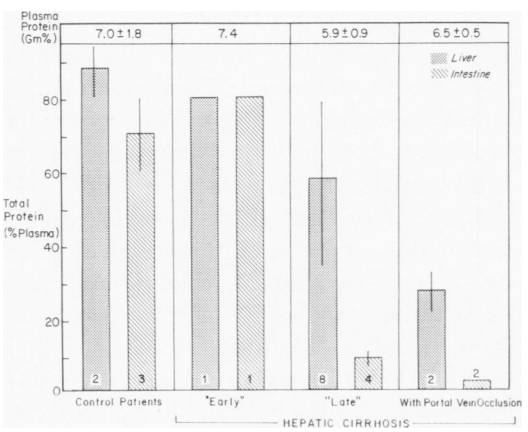


FIG. 7. Total protein in liver and intestinal lymph (mean ± SD) in control subjects and in patients at different stages of hepatic cirrhosis. Numbers at the bottom of each bar represent number of patients studied.

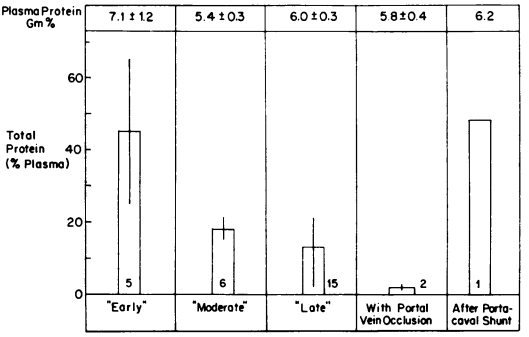


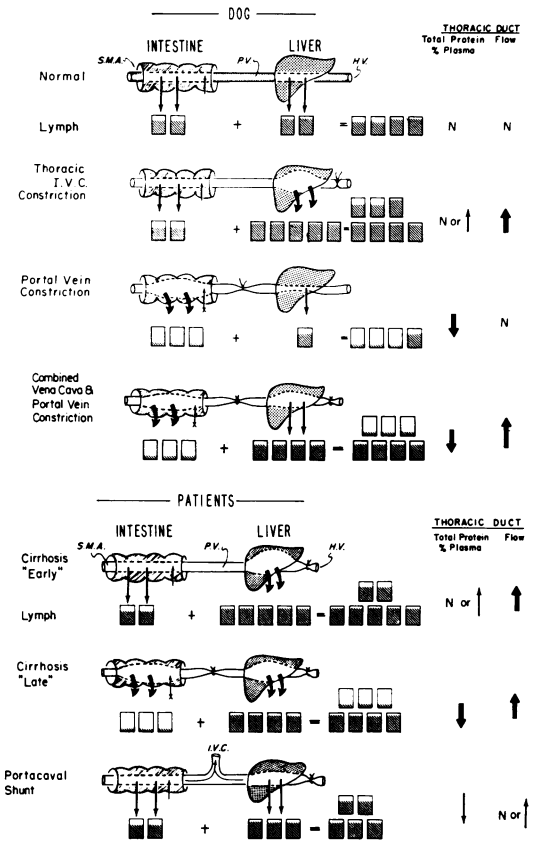
FIG. 8. Total protein in ascitic fluid (mean ± SD) in patients at different stages of hepatic cirrhosis. Numbers on the bottom of each bar represent number of patients studied.

Following a portacaval shunt, protein concentration in thoracic duct lymph increases and flow rate declines. Although postsinusoidal obstruction remains,[40] diversion of portal blood into the cava reduces TDL formation in three ways.

1) Relief of mesenteric congestion decreases formation of capillary filtrate in the extrahepatic portal bed

2) Diversion of portal blood flow lowers hydrostatic pressure in the sinusoid and decreases formation of capillary filtrate in the liver

3) A side-to-side shunt provides addi-



FIGS. 9a and 9b. Schematic diagram demonstrating that pre and posthepatic venous obstruction in dogs produce changes in thoracic duct lymph which resemble those in patients with hepatic cirrhosis.

□—Volume of lymph (shaded area = % protein)
S.M.A.—superior mesenteric artery
P.V.—portal vein IVC—inferior vena cava
H.V.—hepatic veins N—within normal range

tional sinusoidal decompression as the portal vein may function as an outflow tract.

Ascites may disappear after a portacaval shunt. In dogs with posthepatic venous obstruction, side-to-side shunts are more effective than end-to-side shunts in controlling transudation from the liver [35] and in reducing TDL flow.[34, 48] In patients with cirrhosis, when postsinusoidal obstruction predominates, side-to-side shunts are, similarly, more effective. But, when presinusoidal obstruction predominates both end-to-side and side-to-side shunts are equally effective in decreasing transudation from the gut and mesentery.

Determination of portal pressure alone discloses neither the nature of the hemodynamic abnormality nor the origin of excess lymph and ascitic fluid in cirrhosis. Although postsinusoidal obstruction may occur early, a gradual increase in resistance to transhepatic portal blood flow probably develops concomitantly. If hepatopetal flow remains normal or high then portal pressure may rise in the face of elevated intrahepatic pressure. At this stage TDL and ascitic fluid are derived predominantly from the liver. As the disease progresses and presinusoidal obstruction increases, transhepatic portal blood flow decreases, liver function deteriorates and bleeding esophageal varices develop. At this stage TDL and ascitic fluid are derived predominantly from the extrahepatic portal bed.

It is concluded that in hepatic cirrhosis the protein content of both thoracic duct lymph and ascitic fluid reflect the balance between pre- and postsinusoidal obstruction. The divergent effects of these hemodynamic disturbances on lymph formation determine some of the clinical manifestations of the disease.

Summary

Protein content of thoracic duct lymph, liver lymph, intestinal lymph and ascitic fluid was studied in dogs with experimental hepatic and mesenteric venous congestion and compared to patients with hepatic cirrhosis. Experimental posthepatic venous obstruction increases formation of liver lymph and of thoracic duct lymph high in protein. As the lymphatic circulation is overloaded, high-protein liver lymph "weeps" into the peritoneal cavity to initiate ascites. On the other hand, portal vein obstruction lowers the protein concentration in intestinal and thoracic duct lymph.

In patients with hepatic cirrhosis "early" in the disease, increased postsinusoidal re-

sistance predominates and excess liver lymph forms the bulk of thoracic duct lymph. At this stage ascitic fluid is derived from hepatic lymph. As the disease progresses presinusoidal resistance increases, transhepatic portal blood flow decreases, and bleeding esophageal varices occur. Excess low-protein intestinal capillary filtrate now forms the bulk of thoracic duct lymph and ascitic fluid is derived from the bowel and mesentery.

After portacaval shunt and relief of mesenteric congestion, thoracic duct lymph flow decreases and protein concentration rises due to a greater proportion of liver lymph. If the shunt remains patent, postoperative ascitic fluid is probably derived from transected hepatic lymphatics.

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References

1. Ausfes, A. H., Schaffner, S., Rosenthal, W. S. and Herman, B. E.: Portal Venous Pressure in "Pipestem" Fibrosis of the Liver Due to Schistosomiasis. Amer. J. Med. 27:807, 1959.
2. Baggenstoss, A. H. and Cain, J. C.: Further Studies on the Lymphatic Vessels at the Hilus of the Liver of Man. Their Relation to Ascites. Proc. Mayo Cl. 32:615, 1957.
3. Bennett, H. S., Luft, J. H. antd Hampton, J. C.: Morphological Classification of Vertebrate Blood Capillaries. Amer. J. Physiol., 196:381, 1959.
4. Bolton, C.: An Experimental Study of the Pathology of Cardiac Dropsy, and Its Relation to that of Local Venous Obstruction. J. Path. & Bact., 14:49, 1909–10.
5. Bolton, C. and Bernard, W. G.: The Pathological Occurrences in the Liver in Experimental Venous Stagnation. J. Path & Bact., 34:701, 1931.
6. Brauer, R. W.: Liver Circulation and Function. Physiol. Rev., 43:115, 1963.
7. Brauer, R. W., Holloway, R. J., Krebs, J. S. and Leong, G. F.: Changes in Liver Function and Structure Due to Experimental Passive Congestion Under Controlled Hepatic Pressures. Amer. J. Physiol., 197:681, 1959.
8. Cain, J. C., Grindlay, J. H., Bollman, J. L., Flock, E. V. and Mann, F. C.: Lymph from Liver and Thoracic Duct. Surg. Gynec. Obstet., 85:558, 1947.
9. Courtice, F. C.: The Edward Stirling Lectures. Ascites: The Role of the Lymphatics in the Accumulation of Ascitic Fluid. Med. J. Aust., 11:945, 1959.
10. Davidson, C. S.: Cirrhosis of the Liver. Amer. J. Med., 16:863, 1954.
11. DaSilva, L. C. and Pointes, J. F.: Clinical Aspects of Schistosomiasis Mansoni. In Progress in Liver Diseases. Chapter XVII, p. 243, Edited Popper, H. and Schaffner. New York, F. Grune and Stratton, 1965.
12. Dumont, A. E. and Mulholland, J. H.: Flow Rate and Composition of Thoracic Duct Lymph in Patients with Cirrhosis. New Eng. J. Med., 263:471, 1960.
13. Dumont, A. E. and Mulholland, J. H.: Alterations of Thoracic Duct Lymph Flow in Hepatic Cirrhosis: Significance of Portal Hypertension. Ann. Surg., 156:668, 1962.
14. Dumont, A. E. and Witte, M. H.: Contrasting Patterns of Thoracic Duct Lymph Formation in Hepatic Cirrhosis. Surg. Gynec. Obstet., 122:524, 1966.
15. Eisenmenger, W. J. and Nickel, W. F.: Relationship of Portal Hypertension to Ascites in Laennec's Cirrhosis. Amer. J. Med., 20:879, 1956.
16. Gibson, J. B.: Chiari's Disease and the Budd-Chiari Syndrome. J. Path. & Bact., 79:381, 1960.
17. Gibson, J. B. and Smith, J. C.: The Origin of Ascites in Experimental Cirrhosis in the Rat. Amer. J. Path., 41:535, 1962.
18. Glenn, W. W. L., Cresson, S. L., Brauer, F. X., Goldstein, F., Hoffman, O. and Healey, J. E.: Experimental Thoracic Duct Fistula. Surg. Gynec. Obstet., 89:200, 1949.
19. Gorrall, A. G., Bardawill, C. J. and David, M. M.: Determination of Serum Protein by Means of the Biuret Reaction. J. Biol. Chem., 177:751, 1949.
20. Grindlay, J. H., Cain, J. C., Bollman, J. L. and Flock, E. V.: Experimental Studies on Liver and Thoracic Duct Lymph. Minnesota Med., 31:654, 1948.
21. Hales, M. R., Allan, J. S. and Hall, E. N.: Injection-Corrosion Studies in Normal and Cirrhotic Livers. Amer. J. Path., 35:909, 1959.
22. Hoffbauer, F. W., Bollman, J. L. and Grindlay, J. H.: Factors Influencing Pressure in the Portal Vein as Studied in the Intact Animal. Gastroenterology, 16:194, 1950.
23. Hyatt, R. E. and Smith, J. R.: Mechanism of Ascites. A Physiologic Appraisal. Amer. J. Med., 16:434, 1954.
24. Hyatt, R. E., Lawrence, G. H. and Smith, J. R.: Observations on the Origin of Ascites from Experimental Hepatic Congestion. J. Lab. Clin. Med., 45:274, 1955.
25. Johnson, P. C.: Effect of Venous Pressure on Mean Capillary Pressure and Vascular Resistance in the Intestine. Circ. Res., 16:294, 1965.
26. Landis, E. M.: The Capillary Pressure in Frog Mesentery as Determined by Micro-Injection Methods. Amer. J. Physiol., 75:548, 1925–26.
27. Landis, E. M.: Micro-Injection Studies of Capillary Permeability. II. The Relation between Capillary Pressure and the Rate at which Fluid Passes through the Walls of Simple Capillaries. Amer. J. Physiol., 82:217, 1927.
28. Ludwig, K. and Thomsa, W.: Die Anfäge der Lymphgefäbe im Hoden. Sitz-Ber. Wien Akad. Wiss., 44:155, 1861.

29. Madden, J. L., Loré, J. M., Gerold, F. P. and Ravid, J. M.: Pathogenesis of Ascites and the Consideration of Its Treatment. Surg. Gynec. Obstet., **99**:385, 1954.
30. McCarrell, J. D., Thayer, S. and Drinker, C. K.: Lymph Drainage of the Gall Bladder together with Observations on the Composition of Liver Lymph. Amer. J. Physiol., **133**:79, 1941.
31. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis. Arch. Path., **5**:23, 1928.
32. Morris, B.: The Hepatic and Intestinal Contributions to the Thoracic Duct Lymph. Quarterly J. Exp. Physiol., **41**:318, 1956.
33. Nix, J. T., Flock, E. F. and Bollman, J. L.: Influence of Cirrhosis on Proteins of Cisternal Lymph. Amer. J. Physiol., **164**:117, 1951.
34. Orloff, M. J., Goodhead, B., Windsor, C. W. O., Musicant, M. E. and Annetts, D. L.: Effects of Portacaval Shunts on Lymph Flow in the Thoracic Duct. Amer. J. Surg., **114**:213, 1967.
35. Orloff, M. J., Spitz, B. R., Wall, M. H., Thomas, H. S. and Halasz, N. A.: Experimental Ascites IV: Comparison of the Effects of End-to-side and Side-to-side Portacaval Shunts on Intractable Ascites. Surgery, **56**::784, 1964.
36. Orloff, M. J., Wall, M. H., Hickman, E. B. and Spitz, B. R.: Experimental Ascites III: Production of Ascites by Direct Ligation of Hepatic Veins. Surgery, **54**:627, 1963.
37. Pappenheimer, J. R., Renkin, E. M. and Borrero, L. M.: Filtration, Diffusion and Molecular Sieving through Peripheral Capillary Membranes; Contribution to Pore Theory of Capillary Permeability. Amer. J. Physiol., **137**:13, 1951.
38. Pappenheimer, J. R. and Soto-Rivera, A.: Effect of Osmotic Pressure of the Plasma Protein and Other Quantities Associated with the Capillary Circulation in the Hindlimb of Cats and Dogs. Amer. J. Physiol., **152**:471, 1948.
39. Popper, H. and Schaffner, F.: Capillarization of Hepatic Sinusoids in Man. Gastroenterology, **44**:239, 1963.
40. Redeker, A. J., Geller, H. M. and Reynolds, T. B.: Hepatic Wedge Pressure. Blood Flow, Vascular Resistance and Oxygen Consumption in Cirrhosis Before and After End-to-side Portacaval Shunt. J. Clin. Invest., **37**:606, 1958.
41. Rusznyak, I., Foldi, M. and Szabo, G.: Lymphatics and Lymph Circulation: Physiology and Pathology. 2nd Ed. New York, Pergamon Press, 1967, Chapter VI, p. 264.
42. Schilling, J. A., McCoord, A. B., Clausen, S. W., Troup, S. B. and McKee, F. W.: Experimental Ascites. Studies of Electrolyte Balance in Dogs with Partial and Complete Occlusion of the Portal Vein and of the Vena Cava above and below the liver. J. Clin. Invest., **31**:702, 1952.
43. Starling, E. H.: The Influence of Mechanical Factors on Lymph Production. J. Physiol., **16**:224, 1894.
44. Starling, E. H.: The Fluids of the Body. The Herter Lectures. Chicago, W. T. Keener & Co., 1909.
45. Van der Heyde, M. N., O'Keefe, D. and Welch, C. S.: Thoracic Duct Lymph Flow with Variations in Hepatic Hemodynamics. Surgery, **56**:1121, 1964.
46. Volwiler, W., Grindlay, J. H. and Bollman, J. L.: The Relation of Portal Vein Pressure to the Formation of Ascites, an Experimental Study. Gastroenterology, **14**:40, 1950.
47. Wasserman, K., Loeb, L. and Mayerson, H. S.: Capillary Permeability to Micro-Molecules. Circ. Res., **3**:594, 1955.
48. Welch, C. S.: Portal Decompression as a Means to Controlling Ascites. Curr. Surg. Manag. III. Edited by Ellison, E. H., Friesen, S. R. and Mulholland, J. H. Philadelphia, W. B. Saunders Co., p. 293.
49. Witte, M. H., Dumont, A. E., Cole, W. R. and Witte, C. L.: Lymph Circulation in Hepatic Cirrhosis Effect of Portacaval Shunt. Presented at the 49th Annual Session of the American College of Physicians, April 2, 1968, Boston, Massachusetts.
50. Yoffey, J. M. and Courtice, F. C.: Lymphatics, Lymph and Lymphoid Tissue. Harvard Univ. Press, Cambridge, Mass., 1956.

Discussion

Dr. Nathan A. Womack (Chapel Hill): I think this is a splendid study of Dr. Witte, one that deserves commendation. As he has noted, the hepatic sinusoidal endothelial membrane is highly premeable. In electron microscopic studies, as you may recall, there may be seen fenestrations along this membrane as well as probably separation of the cell junction, making it possible for fairly large particles to pass through. The usual rules relating to capillary exchange, therefore, must at times be modified to take care of the exchange of substances from blood to lymph as a result of this unusual permeability.

The sinusoidal endothelium is separated from the hepatic cell by the somewhat irregular space of Disse, which perhaps is the origin of the lymphatic circulation of the liver. Substances from the sinusoidal blood spaces must traverse this space to reach the liver cell and substances from the liver cell into the lymph to be transported to the bloodstream. Liver lymph, therefore, will be rich in protein and it will be sensitive to reentery into the sinusoidal circulation because of pressures and several other mechanisms.

Dr. Witte and his colleagues have demonstrated how sensitive this exchange mechanism is to portal pressure and portal flow. The fact that such an in-