

Significance of Protein in Edema Fluids

C. L. Witte, M. H. Witte, A. E. Dumont

Departments of Surgery, University of Arizona College of Medicine,
Tucson, Arizona and New York University School of Medicine, New York, N. Y.

Lymphology 4 (1971), 29-31

The partition of extracellular fluid between plasma and tissues is largely regulated by the balance of hydrostatic and colloid osmotic (oncotic) pressure gradients across capillary membranes. Normally a small excess of tissue fluid forms, enters lymphatics and returns to the bloodstream. When an imbalance develops between the rate of lymph production and the rate of its return to the systemic venous circulation, edema or effusion appear. Accumulation of edema, however, is not uniform in amount and composition throughout the body and depends on the forces governing capillary filtration, regional differences in capillary permeability, lymph flow and the specific factor tending to perpetuate the edema. Obstruction to lymph return or disruption of capillary integrity (e.g. infiltrating cancer or inflammation) promote effusion or edema high in protein content (so-called "exudate"). On the other hand, increased hydrostatic pressure in semipermeable capillaries promotes excess lymph and ultimately edema or effusion low in protein content (so-called "transudate"). The hepatic sinusoid is unique in its free permeability to plasma protein. Hepatic venous outflow obstruction, accordingly, produces excess hepatic and thoracic duct lymph and eventually ascitic fluid, high in protein.

In his monograph on *The Fluids of the Body* (1), Starling reasoned that increased capillary hydrostatic pressure was initially offset by a fall in tissue oncotic pressure. As the gradient in hydrostatic pressure rises in semipermeable capillary beds a progressively more dilute capillary filtrate forms in tissues. The gradient of colloid osmotic pressure is thereby widened and the enhanced absorbing property of plasma protein partially offsets increased capillary pressure. The capacity to buffer hydrostatic pressure in this way varies considerably in different regions of the body. In the small bowel where tissue protein levels are fairly high (3.5-4.0 g%), a rise of 8-10 cm saline in portal pressure is required to overcome the compensatory fall in tissue oncotic pressure and thereby increase lymph flow. In the extremities, in contrast, tissue protein levels are comparatively low (1.5-2.0 g%) and a rise of only 3-4 cm saline in venous pressure increases lymph flow. Finally, in the liver there is little or no oncotic gradient across the freely permeable sinusoidal membrane. Therefore, a slight increase in the normally low sinusoidal pressure produces a tremendous increase in hepatic lymph production. Accordingly, in hepatic cirrhosis and congestive heart failure, despite some reduction in the absolute plasma oncotic pressure, the gradient in oncotic pressure across semipermeable capillaries is nonetheless greater than normal, compensating for rather than aggravating the tendency toward increased lymph formation from increased capillary pressure (2, 3). Whereas lymphatic obstruction leads to stagnant lymph drainage, lymph

flow is generally greater than normal during venous obstruction. Only in advanced heart failure does systemic venous pressure rise to such heights as to preclude lymph return to the venous circulation. In this situation, "circulatory congestion" evokes a vicious cycle as venous hypertension both enhances lymph production and simultaneously impedes lymph absorption (4).

Under normal circumstances the net balance of hydrostatic and oncotic forces across the capillary wall favors transudation. Hence, when lymphatic channels are choked with cancer or congenitally malformed, edema may arise from failure to transport the small volumes of lymph normally formed in the capillary bed. The amount of edema is then largely determined by the gradient of hydrostatic pressure between capillary and tissue and the protein content of the edema fluid approximates the protein content of normal tissue fluid in the affected area. Treatment of "lymphedema" with diuretic drugs or restriction of salt in the diet is usually ineffective because protein sequestered in the tissues does not ordinarily reenter blood capillaries directly. Despite continued contraction of the plasma compartment, a certain amount of sodium and chloride is obligated to satisfy osmotic requirement of trapped protein. On the other hand, edema fluid that forms after restriction to venous flow is so low in protein that it approximates physiologic salt solution in composition. Dietary salt restriction and diuretic drugs are usually successful in this situation as they contract extracellular fluid and plasma volume and thereby decrease capillary hydrostatic pressure behind the mechanical obstruction. Lymph formation decreases, edema formation ceases, and the reversal in net "Starling forces" across capillaries allows excess tissue fluid to be reabsorbed into the bloodstream. Nevertheless, continued attempts at diuresis are ill-advised in the face of persistent severe venous hypertension (e.g. behind a diseased heart or cirrhotic liver) as dangerous reduction in plasma volume and regional blood flow particularly to the kidneys are inevitable. Operative methods to reduce venous pressure and thereby lymph formation, or alternatively, to increase lymph return are then the only primary courses of action.

Although the pathogenesis of fibroplasia is far from settled, it is curious that in disorders characterized by edema of high protein content fibroplasia is prominent, whereas in edema very low in protein fibroplasia is characteristically minimal. One need only contrast the elephantine extremity with the smooth pitting peripheral edema of congestive heart failure or the hard "garden hose" small intestine of regional enteritis with the swollen boggy bowel of portal hypertension. Edema of the liver, in contrast, is invariably high in protein whether due to lymphatic or venous obstruction, and long-standing Budd-Chiari syndrome, congestive heart failure, and chemical or infectious hepatitis provoke alike desmoplasia and cirrhosis. Perhaps the stimulus to the development of chronic pancreatitis and cholecystitis, retroperitoneal fibrosis, pulmonary interstitial fibrosis and even the healing of wounds arises in the high protein edema of lymphatic obstruction or disruption that over the years promotes extensive scar formation.

It is suggested that measurement of the protein content of edema fluids provides a clue to the underlying derangement in the Starling equilibrium and lymphatic dynamics that initiates and perpetuates fluid accumulation. Furthermore, this information may help to unravel the pathophysiology of unrestrained fibroplasia, the hallmark of a wide variety of chronic diseases.

References

- 1 Starling, E. H.: The Fluids of the Body. University of Chicago Press, Chicago, Ill. 1909
- 2 Witte, C. L., M. H. Witte, A. E. Dumont, W. R. Cole, J. R. Smith: Protein Content in Lymph and Edema Fluid in Congestive Heart Failure. *Circulation* 40 (1969), 623-630
- 3 Witte, C. L., M. H. Witte, K. Kintner, W. R. Cole, A. E. Dumont: Colloid Osmotic Pressure in Hepatic Cirrhosis and Experimental Ascites. *Surg. Gyn. Obstet* (in press)
- 4 Witte, M. H., A. E. Dumont, R. H. Clauss, B. Bader, N. Levine, E. S. Breed: Lymph Circulation in Congestive Heart Failure. *Circulation* 39 (1969), 723-738

C. L. Witte, M.D., Dept. of Surgery, University of Arizona, College of Medicine, Tucson, Arizona

Measurement of Lymph Flow of the Heart*

S. E. Leeds, H. N. Uhley

Departments of Surgery (Experimental Surgery Laboratory) and Medicine, Mount Zion Hospital and Medical Center, San Francisco, California 94115

Lymphology 4 (1971), 31-34

The intrinsic lymphatics of the heart consist of subendocardial, myocardial and subepicardial plexuses. Collecting channels lie in the atrioventricular sulcus and two main trunks drain roughly the left and right sides of the heart (1, 2, 3). Patek (1) noted that these two trunks form a single trunk which lies on the pulmonary artery. Symbas (3) made *in vivo* studies and described separate courses to the mediastinum of the left and the right trunks. A third trunk lies posteriorly and drains part of the posterior myocardium (4). Above the roots of the aorta and pulmonary artery the number of lymphatics pathways and interconnections vary considerably as illustrated by Allison and Sabiston (4).

In our own experience with more than 75 dissections of the mediastinum, the number and location of lymphatics and lymph nodes was variable, particularly at the level exposed through the left 3rd or 4th intercostal space. A single lymph node between the superior vena cava and brachiocephalic artery with two lymphatic channels entering it was encountered in more than half of our animals, however, not infrequently three or four lymph nodes and up to four or five lymphatic channels were seen. When the mediastinum was exposed through a right chest incision (through the 3rd or 4th intercostal space), the lymphatics were less variable. Usually two lymphatics could be seen crossing the right side of the arch of the aorta and cannulation of one of them was carried out at this point. Usually one or two lymph nodes, rarely three or more, were located between the trachea and the superior vena cava, or were in proximity to the arch of the aorta.

* Presented at the Third International Congress of Lymphology, Aug. 27-Sept. 1, 1970, Brussels, Belgium.

Supported by National Institutes of Health, National Heart Institute (H-3180).