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Mechanisms Regulating Interstitial Fluid Volume

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Summary

The present paper deals with the transcapillary fluid balance in hypoproteinemia and increased venous pressure. Interstitial fluid hydrostatic pressure (P_i) was measured by a wick method, and interstitial fluid colloid osmotic pressure (COP_i) was measured in tissue fluid samples obtained from implanted wicks. In rat subcutaneous tissue and skeletal muscle the COP_i was 10 mm Hg and P_i was −1 mm Hg. In hypoproteinemia a marked fall in COP_i was observed in both subcutaneous tissue and skeletal muscle. A fall in plasma COP of 5–6 mm Hg was associated with almost identical fall in COP_i. Similar fall in subcutaneous COP was observed by increasing local venous pressure by 10 mm Hg. Raising the venous pressure on the hind limb did, however, not lead to a fall in skeletal muscle COP_i in intact, freely moving rats. However, when the hind limb was denervated and immobilized an increase of venous pressure caused a fall in skeletal muscle COP_i, similar to that observed in subcutaneous tissue. In both hypoproteinemia and increased venous pressure no rise in P_i could be measured before visible edema was detected. The results indicate that the fall in COP_i will prevent or limit edema formation in hypoproteinemia and when the venous pressure is increased. In addition, in skeletal muscle the muscle pump will protect against increased capillary fluid filtration when the venous pressure is increased, probably by keeping a low capillary pressure during muscle contractions.

Interstitial fluid volume is determined by the net transport of fluid from plasma to the interstitium (F) and the transport of fluid from the interstitium back to plasma by the lymph (L). To maintain constant interstitial fluid volume, lymph flow must equal net capillary filtration (Eq. 1):

$$F = CFC\,(P_c - P_i - \pi_p + \pi_i) = L \qquad \text{Eq. 1}$$

where CFC is the capillary filtration coefficient, P_c is the capillary pressure, P_i is the interstitial fluid hydrostatic pressure and π_p and π_i are the colloid osmotic pressure in plasma and interstitium, respectively. If not in a steady state, the change in interstitial fluid volume (ΔV) should be:

$$\Delta V = \int (F - L)\,dt \qquad \text{Eq. 2}$$

$$\Delta V = \int CFC(P_c - P_i - \pi_p + \pi_i - L/CFC)\,dt \qquad \text{Eq. 3}$$

It should be noted that L/CFC in Eq. 3 has the dimension of pressure, for instance mm Hg, and is thereby directly comparable to the hydrostatic and colloid osmotic pressures.

The well known fact that a rise in capillary pressure (P_c) of 10–15 mm Hg or fall in plasma colloid osmotic pressure (π_p) of about 10 mm Hg do not lead to edema must imply compensatory changes in one or more of the remaining factors in Eq. 3. It has been emphasized by *Guyton* and collaborators (5) that a rise in interstitial fluid pressure should represent the major edema opposing factor in subcutis. Their results, based on measurements with implanted capsules, indicate a low compliance in subcutaneous tissue. A marked rise in interstitial fluid pressure caused by a small volume rise should thereby counteract further fluid filtration.

Several studies have shown a fall in lymph protein concentration when the venous pressure is increased due to a relative greater increased filtration of water than of proteins. Thus, if lymph protein concentration is representative for interstitial fluid, a fall in interstitial colloid osmotic pressure may contribute to the edema prevention. The third factor, an increased lymph flow will also protect the tissue from large volume rise. As pointed out by *Guyton* (5) the net filtration pressure which can be compensated by lymph flow can be estimated by measuring maximal lymph flow and CFC (see Eq. 3).

I will now refer to some experiments where we have studied the relative contribution of the interstitial fluid colloid osmotic and hydrostatic

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pressures in the edema prevention during hypoproteinemia and increased venous pressure.

Interstitial fluid colloid osmotic pressure was measured on fluid samples obtained from nylon wicks implanted in subcutaneous tissue and muscle in rat. A 3–5 cm long nylon wick was sewn into the tissue and after 1 hour implantation the wick was taken out and the protein concentration and COP in the wick fluid was determined (3). The interstitial fluid hydrostatic pressure was measured with a "wick-in-needle" method (4): A hypodermic needle, diameter 0.6 mm, provided with a 2–4 mm long sidehole and filled with multifilamentous nylon threads was inserted into the tissue. Adding and withdrawal of tissue fluid by clamping and decompression of the polyethylene catheter connecting the needle to the transducer dome indicated a satisfactory fluid communication between the needle and the tissue fluid. In subcutaneous tissue the colloid osmotic pressure was 10 mm Hg and the hydrostatic pressure 0 to −1 mm Hg. Later, it became apparent that the wick fluid does not represent normal, undisturbed interstitial fluid (3). A marked inflammation due to the wick insertion, demonstrated with labelled albumin, showed that most of the proteins in the wick fluid was derived from plasma the first 30 minutes after wick insertion. Furthermore, when this inflammation response was suppressed by anti-inflammatory drugs as indomethacin or cyproheptadine, the protein concentration and colloid osmotic pressure in the wick fluid after 1 hour implantation was significantly lower. These observations raised questions about the validity of the wick method. Several other observations indicate, however, that the implanted wick gives meaningful information about colloid osmotic and hydrostatic pressure in the interstitium. It was observed that in the case of low capillary permeability the fluid content in the wicks was reduced during the 1 hour period of implantation, and this was associated with a large negative wick hydrostatic pressure. In all cases the sum of wick fluid colloid osmotic pressure and negative wick hydrostatic pressure was the same, about 11 mm Hg, representing the tissue forces pulling fluid out from the capillaries. The relative contribution of colloid osmotic and hydrostatic pressure is more uncertain. Wick hydrostatic pressure of −7 mm Hg and colloid osmotic pressure of 4 mm Hg in a condition with "normal" capillary permeability agree with measurements with implanted capsules in dog (5).

The following observations suggest, however, that the wick behaves like an implanted colloid osmometer and that wick fluid colloid osmotic pressure of 10 mm Hg and wick hydrostatic pressure of 0 to −1 mm Hg represent the condition in normal, undisturbed interstitium (3):

1. In the case of low capillary permeability, negative wick fluid pressure was not observed when the wick was preloaded with plasma before implantation.
2. Thinner wicks (volume about 1/3 of standard wicks) showed a colloid osmotic pressure of 10 mm Hg and hydrostatic pressure of −1 mm Hg, independent of the capillary permeability to proteins.
3. In the situation with a large negative wick pressure, the interstitial fluid pressure measured with the "wick-in-needle" method was zero or slightly negative, −1mm Hg, indicating that negative wick pressure is caused by a colloid osmotic disequilibrium between the wick and the surrounding interstitium.
4. Using implantable colloid osmometers, impermeable and permeable to plasma proteins, gave values of 10 and −1 mm Hg, respectively in agreement with the hypothesis (6).

Now, let's see what happens when plasma colloid osmotic pressure is reduced and venous pressure increased. Hypoproteinemia was produced in rats by daily injections of aminonucleoside which is nephrotoxic, producing heavy proteinuria. When the plasma protein concentration was falling, a marked fall in interstitial fluid protein concentration was observed (1). A fall in plasma colloid osmotic pressure from 18 to 13 mm Hg was accompanied by a fall in interstitial fluid colloid osmotic pressure from 8 to 3 mm Hg (Fig. 1). This implies unchanged net transcapillary colloid osmotic pressure at this stage of hypoproteinemia and thereby protects the tissue from

large volume increase and edema. These results refer to subcutis, but similar results were obtained from skeletal muscle.

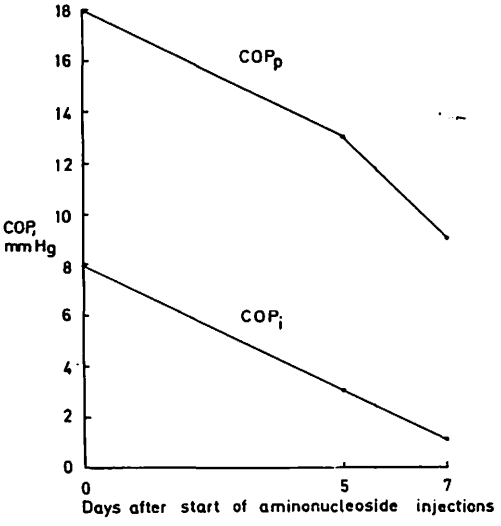

Fig. 1 Colloid osmotic pressure in plasma (COP_p) and interstitial fluid (COP_i) during aminonucleoside nephrosis.

In another group of rats we studied the effect of increased venous pressure upon the interstitial fluid colloid osmotic and hydrostatic pressure (2). Increased venous pressure was produced on the hind limbs of rats by ligating the inferior caval vein and iliac veins. One to three days later we measured during anesthesia interstitial fluid colloid osmotic and hydrostatic pressure and the femoral venous pressure. In subcutis no edema was observed at venous pressures below 12 mm Hg. This is well explained by the marked fall in interstitial fluid colloid osmotic pressure which will oppose the large net filtration pressure caused by the increased venous pressure (Fig. 2). Interstitial fluid hydrostatic pressure did not contribute much to the edema prevention at this stage. Only when clinical edema was present did the interstitial fluid rise by 2–3 mm Hg, indicating that a rise in interstitial fluid pressure will only limit an already exisiting edema.

These experiments have shown that a fall in interstitial fluid protein concentration and colloid osmotic pressure is the most important edema preventing mechanism in subcutis of rats. To maintain the new steady state with low protein concentration in the interstitium there must be a continuous increased lymph flow to take care of a normal or increased transcapillary protein transport. It is therefore not only a dilution but a washing out of proteins from the interstitium back to plasma by the lymph.

In skeletal muscle, the muscle pump seems to protect against a rise in capillary pressure when the venous pressure is increased. As opposed to subcutis, no marked fall in interstitial fluid colloid osmotic pressure of skeletal muscle was

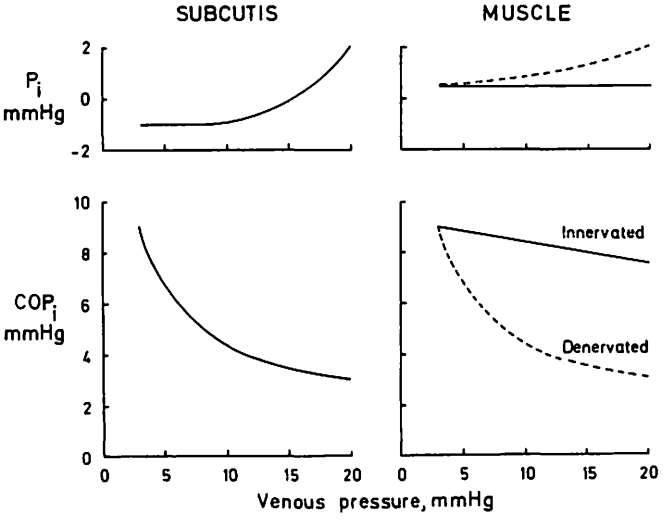

Fig. 2 Relationship between venous pressure and interstitial fluid colloid osmotic (COP_i) and hydrostatic pressure (P_i). Left panel: Subcutis. Right panel: Skeletal muscle.

observed when the venous pressure on the hind limb was increased. On the other hand, when the muscles on the hind limb was motorically denervated and the rat immobilized in a perpex cylinder, a fall in interstitial fluid colloid osmotic pressure similar to that in subcutis was observed (Fig. 2). The most likely explanation would seem to be that the pressure in the femoral vein is lower in the moving limb than that measured during anesthesia. However, this is unlikely since edema was observed in subcutis, but not in muscle. Therefore, the pressure in capillaries and veins within the muscle seems to be kept low in spite of increased pressure in the femoral veins. This might be explained by an increased outflow of blood from the muscle capillaries and venules during muscle contraction and a fall in capillary pressure to normal level in the subsequent relaxation period, maintaining a normal transcapillary fluid balance. Thus, in the case of increased venous pressure, the effect of the muscle pump must be added to the edema safety factors found in subcutis.

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Discussion

Szabó: We are working on the same general lines as Dr. Fadnes and Dr. Aukland. Many of our results agree but some do not. We have observed even after moderate decreases in plasma colloid osmotic pressure great drops in the colloid osmotic pressure of the tissue fluid. On the other hand effective capillary filtration pressure is much lower than 15 to 17, mostly because the sum of negative hydraulic and of colloid osmotic pressures in the tissues fluid is higher than generally assumed. Accordingly, the effective capillary pressure is in order of 8 to 10 mm Hg. We have looked for the correlation between venous and tissue fluid pressure. Tissue fluid pressure was measured inside the Guyton's capsule and the results were different from those obtained by the wick technique. Measured with the wick method, tissue fluid hydraulic pressure increased with the rise of venous pressure from zero or –1 mm Hg to +2 Hg. Accordingly, the compensating effect of tissue fluid pressure changes and its regulating effect on capillary filtration when capillary pressure is increased will be only a small one. Within the capsules we measured pressures as low as –7 or –5 mm Hg and it increased to +1 or + 2 mm Hg. This means, that there is a range of about 9 mm Hg to compensate the effects of increased venous pressure. Consequently, there are four factors which contribute to ward off the effect of increased venous and capillary hydraulic pressures: 1/Increased plasma oncotic pressure (as a consequence of increased water filtration from the capillaries); 2/ Elevated tissues fluid hydraulic pressure; 3/ Decreased colloid-osmotic pressure in the tissue fluid; 4/ Increased lymph flow.

Fadnes: Do you think that what you measured was the effect of increased venous pressure on the hydrostatic pressure and not an effect on colloid osmotic pressure?

Szabó: This is a possibility, but it is difficult to see how a colloid-osmotic pressure gradient of 5 to 7 mm Hg could exist between intra- and extracapsular fluids.

Fadnes: The fall in interstitial fluid colloid osmotic pressure might raise the capsule pressure?

Szabó: There is an observation, which speaks indirectly against this assumption. We have found a good correlation between venous and capsular hydraulic pressure, but no correlation between venous pressure and tissue fluid colloid osmotic pressure.

Fadnes: As pointed out by Dr. Wiederhielm the tissue membrane surrounding the capsule might behave as a semipermeable membrane. If so, fall in intertitial fluid colloid osmotic pressure with increasing venous pressure will result in a rise in capsule fluid hydrostatic pressure. Measurements of wick hydrostatic and colloid osmotic pressure using wicks preloaded with saline and plasma indicate that the implanted wick behaves as a colloid osmometer. Our observations indicate that the wick fluid COP of 10 mm Hg and wick hydrostatic pressure of −1 mm Hg reflect the true interstitial fluid pressure. Recently, we have compared the concentration and COP in wick fluid from subcutaneous tissue and local lymph in rabbits with increasing venous pressure. The wick fluid COP was not different from that in lymph, indicating that the wick fluid reflects the COP in the interstitium. The albumin/globulin ratio was, however, lower in wick fluid than in lymph, probably because of the permeability rise due to the wick insertion. Therefore, the wick method seems not suitable for studying transcapillary transport of various macromolecules.

Nicolaysen: One question concerning this observation of very little or no change in the interstitial hydrostatic pressure with elevated venous pressure. At the same time you found a rather dramatic decrease in protein concentration in wick fluid which you said must mean that there is an increased transvascular flux of fluid and which again must mean that the lymph flow has increased. I would like your comment to this point: What is the driving force then for the increased filling of the lymphatics if there is no change in the interstitial hydrostatic pressure. How do you then get this compensating increase in lymph flow?

Fadnes: In skeletal muscle we found a less than 10% rise in interstitial fluid volume when plasma COP was decreased by 5–6 mm Hg. The interstitial fluid protein concentration was reduced to half that of normal. This means that the protein transport from the interstitium back to plasma by the lymph must be increased. However, we do not know what is the driving force for the increased lymph flow.