Interstitial Fluid Pressure
IV. ITS EFFECT ON FLUID MOVEMENT THROUGH THE CAPILLARY WALL

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ABSTRACT
Fluid movement through the capillary membrane has been measured in the lower legs of dogs by using implanted, perforated capsules as internal plethysmographs. Utilizing this procedure it was possible to compare the effects of changes in interstitial fluid pressure with the effects of changes in venous pressure and arterial pressure on movement of fluid through the capillary membrane. A decrease in interstitial fluid pressure of 1 mm Hg increased the filtration of fluid out of the capillaries 1.20 as much as did 1 mm Hg increase in venous pressure. The filtration coefficient for fluid movement through the capillary wall per unit change in interstitial fluid pressure was 0.058 µliter/min per mm Hg per g of tissue. This value is in the same range as filtration coefficients that others have determined following changes in capillary pressure.

ADDITIONAL KEY WORDS
interstitial fluid pressure body fluids fluid movement across capillary wall tissue pressure capillary membrane venous pressure dog

When Starling, 70 years ago, enunciated the basic principles of the balance of forces at the capillary membrane for control of fluid movement through the capillary wall, he pointed out that four different factors, capillary pressure, interstitial fluid pressure, plasma colloid osmotic pressure, and tissue colloid osmotic pressure, all affect the movement of fluid through the capillary wall (1). Yet, he was able to measure only the plasma colloid osmotic pressure, and the other factors of this hypothesis were inferred theoretically. Thirty years later, Landis added a second measurement, that of capillary pressure, and demonstrated the reciprocal relationship between plasma colloid osmotic pressure and capillary pressure on movement of fluid through the capillary membrane (2, 3). In still later years, the colloid osmotic pressure of tissue fluids has been estimated for the normal person (4) or animal (5, 6) from data obtained using radioactive tagged albumin. However, there has remained one factor of Starling’s original hypothesis, interstitial fluid pressure, that has not been clearly associated with the rate of fluid movement through the capillary membrane.

During the past few years we have used a method for measuring interstitial fluid pressure based on pressures measured in perforated capsules implanted in tissues. We have presented evidence in previous papers (7, 8) to support our belief that our measurements of interstitial fluid pressure are valid. Though we recognize that some investigators do not accept our measurements of interstitial fluid pressure as equivalent to true interstitial fluid pressures, nevertheless, recent experiments have demonstrated that changes in the measured interstitial fluid pressure correlate very closely with changes in rate of movement of fluid into or out of the capillaries. In this paper, we present data from these experiments illustrating this high degree of correlation.

Methods
The basic animal preparation used in these experiments was the same as that reported by us.
previously (7, 8, 9). Briefly, perforated, hollow spherical capsules, approximately 1.5 cm in diameter, were implanted in the subcutaneous tissue of the lower leg of medium to large dogs, and a period of 4 to 8 weeks was allowed for healing. At the end of this time, fibrous tissue had grown through the perforations and lined the inside of the cavity in the capsule. The central portion of the cavity became filled with approximately 1 ml of fluid.

Primary attention was directed toward measurement of the rate of fluid filtration into the cavity of the capsule or absorption of fluid from the cavity under different dynamic states. To measure the rate of fluid filtration or absorption, the apparatus shown in Figure 1 was used. A clear vinyl catheter, having an inside diameter of 0.7 mm, was connected to a 22-gauge needle which was inserted through the skin and through one of the perforations of the capsule to the inside of the cavity. The catheter was filled with darkly dyed (T-1824 dye) Tyrode's solution. This tube was placed in a slit between two metal bars so that light on one side of the slit had to pass through the tube to reach the other side. Then the slit and tube were placed over the bed of a servo recorder as shown in the figure. An air bubble was introduced into the catheter where it lay over the pen drive. Connected to the pen of the servo recorder was a light source that lay on one side of the slit and a photocell on the other side arranged so that when the air bubble moved in the catheter, an appropriate electrical signal from the photocell was transmitted to the servo drive and caused the pen of the recorder to follow the movement of the air bubble. Thus, as illustrated in Figure 1, when minute quantities of fluid flowed out of the cavity of the implanted capsule or flowed into the cavity, a record of this fluid movement was recorded on the chart. Movement of as little as 1 mm³ of fluid per 10 min could be recorded. In effect, therefore, the hollow implanted capsule was used as an implanted plethysmograph to record movement of fluid out of the capillaries into the cavity or from the cavity back into the capillaries.

Note also in Figure 1 the arrangement by which either vacuum or pressure could be applied to the fluid inside the cavity of the capsule. A leveling bulb was attached to the end of the catheter, and this was adjusted to a level at which there would be flow of fluid neither into the capsule nor out of it. The level of the fluid in the bulb ordinarily had to be 5 to 10 cm below the level of the capsule because the control pressure inside the capsule was 5 to 10 cm H₂O negative with respect to atmospheric pressure. However, vacuum or pressure could then be applied to the upper surface of the fluid in the leveling bulb to increase or decrease the pressure inside the cavity of the capsule with respect to its original control value. To determine how much the flow in the tube could affect transmission of pressure from the leveling bulb to the interior of the capsule, the tip of the needle was placed in a beaker of Tyrode's solution, and a known pressure was applied to the other end of the catheter. The conductance of fluid through the needle and catheter was 52 μliter/min per mm Hg, which was over 500 times as great as the conductance recorded in any of the experiments. Therefore, one can make the assumption that, within the limits...
of experimental error, the pressure applied to the fluid in the leveling bulb was also applied to the interior of the capsule. It could also be calculated that the maximum error caused by this assumption was never greater than 0.02 mm Hg, which represents only a small fraction of the potential error of measurement.

It was pointed out in a previous publication that fluid moves relatively freely between the cavity inside the capsule and the spaces between the cells outside the capsule. Because of this effect it was necessary in these experiments not to create a pressure difference between the tissue spaces outside the capsule and the cavity of the capsule. To do this, a plastic chamber was placed over the leg as shown in Figure 1 and made air-tight to the leg both above and below the implanted capsule by means of rubber diaphragms. Whenever the pressure inside the capsule was increased, the pressure surrounding the leg was increased an equal amount. Likewise, whenever the pressure inside the capsule was decreased, a similar decrease in pressure was effected surrounding the leg. It was assumed that the pressure in the chamber was transmitted throughout the tissues, which seemed reasonable because the tissues at no time were turgid with edema.

In many experiments, the effects of changes in venous and arterial pressure on movement of fluid through the capillary wall were compared with the effects of changes in interstitial fluid pressure. To do this, the femoral artery and vein supplying the leg were isolated in the femoral triangle, and an occlusive tourniquet was placed around the remainder of the leg beneath these two vessels. Arterial pressure could be reduced or venous pressure elevated by appropriate compression of the respective vessels. These pressures were measured peripheral to the compression through 24-gauge needles inserted into the vessels and connected to Statham strain gauges recording on a Minneapolis-Honeywell Visicorder. The dogs were anesthetized with sodium pentobarbital (25 mg/kg iv) during the periods of recording.

Results

Effect of Decreased Interstitial Pressure

Figure 2A illustrates the typical effect of applying different degrees of negative pressure to the cavity of a capsule. Initially, the capsule pressure was at a control value of −6 mm Hg. During this period there was fluid movement neither into nor out of the capsule. Then an additional 10 mm Hg of negative pressure was applied to the cavity for 16 minutes. At this point fluid started to move out of the capsule. Figure 2B illustrates the movement of fluid out of an implanted capsule caused by a decrease in venous pressure.
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pressure was applied to the capsule. Immediately upon application of this negative pressure there was a rapid phase of fluid movement out of the capsule lasting only a few seconds. We interpreted this rapid movement to be caused by expansion of the blood vessels inside the capsule. This is the same effect that Pappenheimer and Soto-Rivera (10), Mellander (11), Johnson and Hanson (12), and many others recorded when studying the effect of blood pressure changes on fluid movement through the capillary membrane; all of these authors have interpreted the initial rapid movement of fluid to result from changes in vascular volume.

Following the rapid phase of fluid movement was a slow, steady movement of fluid. This we interpreted as actual transudation of fluid through the capillary membrane. The results of Pappenheimer, Mellander, and Johnson also showed the same characteristics, and they, too, interpreted this slow phase of fluid movement to be caused by fluid transudation through the capillary membrane. That this fluid movement is not caused by further expansion of the blood vessels is indicated by several facts. First, the steady phase of fluid movement continues for hours without significant decrement in flow. Second, the steady flow within 20 min usually averages about 2,000% of the initial rapid flow, while Forciuncula and co-workers' data on delayed compliance of veins (13) indicated only a 30% further increase in volume in 20 min.

At the end of each 4 min during the experiment of Figure 2A, the negative pressure was increased an additional 10 mm Hg. Each time there was a rapid phase of fluid movement followed by a phase of steady movement. The rate of fluid movement out of the cavity as indicated by the slope of the curve increased progressively. Figure 3 shows the relationship of rate of flow out of the capsule to the degree of negative pressure for five experiments chosen at random from over 100 separate experiments, showing that within reason a linear relationship exists in each experiment between flow of fluid from the capsule and degree of negative pressure. This was also the effect observed by Pappenheimer and Soto-Rivera (10), Mellander (11), Johnson and Hanson (12), and others in plethysmographic and gravimetric studies of fluid filtration through the capillary membrane when the blood pressure was altered.

Filtration Coefficient for Fluid Movement through the Capillary Wall

The rate of fluid movement outward through the capillary wall under the influence of negative pressure in the capsule was measured 30 times in 13 separate experiments, and the average value for filtration of fluid was 0.081 (± 0.018 SD) liter/min per mm Hg. At the end of six of these experiments, the capsules were removed from the legs and the mass of tissue grown to the inside of the capsule was weighed. The average mass of tissue in the capsules was 1.41 (±0.30 SD) g. Using this value and the above value for the rate of
filtration, the average filtration coefficient for the mass of tissue inside the capsule was calculated to be 0.058 μl/min per mm Hg per g of tissue.

Effect of Increased Interstitial Fluid Pressure

A very surprising effect occurred when the interstitial fluid pressure was increased above the control value: there was only a transient effect on the movement of fluid through the capillary membrane. Figure 4A illustrates the results of one of the experiments. In this case the intracapsular pressure was increased by 25 mm Hg. The curve in Figure 4B demonstrates for comparison the effect in the same animal when the intracapsular pressure was decreased by 25 mm Hg. Note that even though the decrease in intracapsular pressure caused rapid filtration of fluid out of the capillaries, the very marked increase in pressure caused only transient absorption of fluid followed by complete cessation of absorption within 10 min. By way of contrast, in five experiments in which negative pressures of at least —20 mm Hg were applied for 40 to 70 min, movement of fluid out of the capsules was still occurring at the end of this time at rates within 20% of the initial rates.

Though this failure of positive pressure to cause continued absorption of fluid was surprising, it is an effect that is predicted by the concept of the vascular waterfall (14). That is, when pressure is applied to the outside of the collapsible veins, the pressure inside the veins must rise at least to equal the outside pressure before blood will resume flow. Therefore, increased external pressure on the tissues increases the pressures inside the veins (and consequently in the capillaries) at the same time that it increases the pressure in the interstitial fluid. As a result, the external pressure causes little increase in pressure gradient across the capillary membrane to cause fluid movement from the intracapsular space into the capillaries. This same experiment was repeated 10 times, and in no single instance was there sustained absorption of fluid. When negative pressure was applied to the tissues, one might have expected decreased pressure inside the veins. However, the veins central to the plethysmographic chamber were still
exposed to normal atmospheric pressure, which kept the pressure in these veins at least as great as atmospheric pressure, again because of the waterfall effect. Obviously, the more peripheral venous pressure could not decrease below the central venous pressure. Therefore, in contrast to the very great effect that positive external pressure has on venous pressure, negative external pressure has very little effect.

Comparison of the Effect of Interstitial Fluid Pressure Changes and Venous Pressure Changes

In 17 different experiments, the movement of fluid through the capillary membrane was studied following increases in venous pressure caused by compression of the isolated femoral vein, as explained in Methods. An increase in venous pressure caused initial rapid movement of fluid out of the capsule, which was interpreted as an increase in intracapsular vascular volume for reasons explained earlier. This was followed by slow, steady fluid movement that was interpreted as filtration of fluid out of the capillaries. The mean quantitative value recorded in these experiments showed filtration at a rate of .068 (±.014 SD) μliter/min per mm Hg elevation in venous pressure.

In 7 animals rates of filtration were measured both following application of increased negative pressure to the interstitial fluid and also following increased venous pressure. Figure 2A illustrates the effect of negative interstitial pressure and 2B the effect of increased venous pressure in the same animal. In three of the experiments the effect of changes in interstitial fluid pressure was measured first and the effect of changes in venous pressure was measured immediately thereafter. In four of the experiments the reverse procedure was used with no discernable difference in the results. The results from two of these experiments are shown in Figure 5. The average filtration rate following changes in venous pressure was .064 (±.015 SD) μliter/min per mm Hg change in venous pressure. The average filtration rate following changes in interstitial fluid pressure was .077 (±.018 SD) μliter/min per mm Hg. From these data, one can see that a change in interstitial fluid pressure caused 1.20 times as much effect on fluid filtration as did a similar change in venous pressure. This difference was to be expected because capillary pressure is determined about 4/5 by venous pressure and about 1/5 by arterial pressure. Therefore, when venous pressure is increased without simultaneously increasing arterial pressure, the capillary pressure increases only about 4/5 as much as does venous pressure.

Effect of Decreased Arterial Pressure

In 11 experiments the arterial pressure was reduced suddenly from its control value (105 to 135 mm Hg) to a value approximately half the control level (40 to 75 mm Hg). The venous pressure was monitored continuously, and adjustments were made in the degree of compression of the vein to keep venous pressure precisely constant. Figure 6B illustrates
the effect observed in these experiments. The results in the 11 experiments were so nearly alike that the curves could be superimposed almost exactly onto each other. Immediately upon decreasing the arterial pressure, an initial disturbance was recorded, presumably caused by decrease in the blood volume in intracapsular vessels. However, the subsequent rate of fluid absorption was usually too little to be measured. This effect, shown in Figure 6B, is contrasted with the marked effect of increasing the venous pressure in the same animal, illustrated in Figure 6A.

In six of the experiments, this experiment was designed so that the arterial pressure was decreased in steps of 20 mm Hg at a time, but the change in fluid movement was too small to be detected.

Estimations of Capillary Pressure by the Isovolumetric Method

Mellander has used an isovolumetric method for estimating the relative effects of arterial pressure and venous pressure on fluid transudation through the capillary wall (11), and Pappeneimer and Soto-Rivera (10) and Johnson and Hanson (12) have used isogravimetric methods for the same purpose. These procedures can be utilized to estimate capillary pressure in the following manner: the venous pressure is progressively elevated, and at the same time the arterial pressure is decreased sufficiently to keep the venous pressure rise from increasing the volume or weight of the leg as a result of fluid filtration out of the capillaries. This elevation of venous pressure and reduction of arterial pressure are continued until the two pressures approach an equilibrium point, which is considered to be an estimate of capillary pressure. This type of experiment was attempted in the present study in 11 dogs. However, since arterial pressure had almost no effect on transcapillary movement of fluid in these experiments, one can readily understand that the equilibrium pressure at which the two pressures approached each other under isovolumetric conditions was essentially equal to venous pressure. Therefore, one would estimate from

A, movement of fluid caused by increasing the venous pressure. B, movement of fluid into the same capsule caused by decreasing the arterial pressure to approximately one half of the control value, showing only a transient disturbance but no prolonged absorption of fluid.

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these results that the capillary pressure is very nearly equal to venous pressure. Obviously, this is a very improbable result; the difference between our results and those reported previously can possibly be explained by the fact that our preparation had been subjected to very little surgical trauma, in contrast to the preparations of the previous studies which were isolated from the body and perfused extracorporeally.

Discussion

The primary importance of these studies is that they confirm Starling's hypothesis that changes in interstitial fluid pressure can affect movement of fluid through the capillary membrane in the same way as do changes in capillary pressure, plasma colloid osmotic pressure, and interstitial fluid colloid osmotic pressure. Indeed, it was particularly significant that a decrease in interstitial fluid pressure increased capillary transudation 1.20 times as much as did an equal increase in venous pressure. This is the effect to be predicted for the following reasons. If we assume that an increase in venous pressure causes the capillary pressure to increase 80% as much, then we can calculate that a decrease in interstitial fluid pressure increases capillary transudation 0.96 times as much as does an equal increase in capillary pressure. Therefore, we can estimate from these experiments that a decrease in interstitial fluid pressure causes almost exactly the same effect on fluid movement through the capillary membrane as does an equal increase in capillary pressure.

The filtration coefficient that we found in these experiments, based on unit mass of tissue inside the capsules and on the change in interstitial fluid pressure, was 0.058 μliter/min per mm Hg per g. This value compares favorably with values determined by others following increased capillary pressure. For example, the value 0.061 μliter/min per mm Hg per g was calculated by Brown et al. for the capillaries of the whole human body (15) from data obtained during venous congestion, and the value 0.140 μliter/min per mm Hg per g was found in isogravimetric studies by Pappenheimer and Soto-Rivera for the capillaries of the hind leg of the dog, and 0.105 μliter/min per mm Hg per g was found for the hind leg of the cat (10). The importance of the filtration coefficient that we have determined is not the preciseness of its measurement, because obvious artifacts can occur in all such measurements as these. Rather, the measurement is important because it shows that the rate of fluid movement through the capillary membrane caused by decreased interstitial pressure is, within the limits of accuracy of available measuring techniques, in the same range as the rate caused by an equal increase in capillary pressure.

An especially surprising result of these studies was the fact that decreasing the arterial pressure failed to cause significant absorption of fluid by the capillaries. This result could have been caused by any one or combination of many different factors, some of which are the following.

First, autoregulation of blood flow could cause such an effect, because in autoregulating tissues a decrease in arterial pressure is followed by compensatory arteriolar dilatation, which would return the capillary pressure nearly to normal despite the marked fall of arterial pressure. Conditions in these experiments were ideal for autoregulation because there had been no surgery near the tissues surrounding the measurement capsule, and the vascular system was not perfused artificially. It is known that such an undisturbed circulation autoregulates maximally (16).

Second, the presence of a vascular waterfall immediately downstream from the capillary could account for failure of a decrease in arterial pressure to cause absorption of fluid by the capillaries. The reason for this is that the pressure immediately above a vascular waterfall has been shown by Permutt and Riley to remain essentially constant despite changes in flow and also despite changes in pressure head far upstream from the waterfall (14). There was evidence in the present experiments that a partial vascular waterfall does exist between the capillaries and the veins because an increase in venous pressure...
from 0 to 10 mm Hg caused less effect on capillary fluid transudation than did an increase in venous pressure from 10 mm Hg to 20 mm Hg. This difference can be observed in Figure 5, which shows that the initial rise in venous pressure was much less effective in promoting fluid transudation through the capillary membrane than were subsequent increases in venous pressures.

The third possibility is that capillary pressure is so near to venous pressure that alterations in arterial pressure would not be expected to affect capillary pressure significantly. We would have expected at least some measurable effect of decreased arterial pressure on fluid movement through the capillary membrane if the capillary pressure had been more than 5 to 10 mm Hg greater than venous pressure. Therefore, this insignificance of effect of decrease in arterial pressure on fluid absorption into the capillaries is an indication that the normal capillary pressure is not far above venous pressure. This result fits well with Johnson's measurements, which estimated capillary pressure in the gut to be only 7 mm Hg greater than venous pressure (17).

References

Circulation Research, Vol. XIX, December 1966
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*Circ Res.* 1966;19:1022-1030
doi: 10.1161/01.RES.19.6.1022

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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