Interstitial Fluid Pressure: III. Its Effect on Resistance to Tissue Fluid Mobility

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ABSTRACT

The resistance to fluid mobility in the interstitial fluid spaces has been measured between perforated catheters inserted into the subcutaneous abdominal tissues of the dog and between perforated capsules implanted in the tissues 1 month previously. When the pressures in the catheters or perforated capsules were less than atmospheric pressure, the resistance to fluid movement was almost infinite, but when the pressures were increased almost to or above atmospheric pressure the resistance usually decreased more than 100,000-fold, indicating a suddenly increased size of the tissue spaces.

The shape of the pressure-volume curve relating (a) interstitial fluid pressure to (b) volume of mobile interstitial fluid was calculated from pressure-conductance curves recorded in these experiments. On comparing this pressure-volume curve with a previously measured pressure-volume curve of the entire interstitial fluid compartment, two important points were observed: first, both curves exhibit a sudden increase in volume when the interstitial fluid pressure rises above atmospheric pressure. Second, the mobile interstitial fluid volume approaches zero when the interstitial fluid pressure falls below atmospheric pressure while the measured volume is still very great. It is postulated that this difference is caused by entrapment of large amounts of water in a relatively immobile state in the gelatinous matrix of the ground substance filling the interstitial spaces.

ADDITIONAL KEY WORDS

tissue pressure interstitial fluid volume pressure of tissue fluids
resistance of interstitial fluid edema collapsible tubes
subcutaneous tissues anesthetized dogs body fluids

In recent experiments utilizing two different procedures of measurement, we have estimated the interstitial fluid pressure under both normal and edematous conditions. An unexpected result of these experiments has been that the interstitial fluid pressure under normal conditions, as measured in the subcutaneous tissues and in muscle, ranges from about — 4 to — 8 mm Hg with respect to the atmospheric pressure. Conversely, the pressure has always been slightly positive in edema; this fact leads to the concept that edema results whenever the pressure beneath the skin becomes greater than the atmospheric pressure pressing against the skin from the outside. It also leads to the conclusion that under normal conditions there is an absorptive force which tends to keep only a minimum amount of free fluid in the tissues.

Upon further examination of this same concept we have measured the pressure-volume curve of the tissue spaces and have found the compliance of the tissue spaces to be very slight when the interstitial pressure is less than atmospheric pressure but very large when the interstitial fluid pressure is greater than the atmospheric pressure. That is, in the negative pressure range the spaces seem to be compressed to a minimum volume that cannot readily be compressed further by additional negative pressure. On the other hand, in the positive pressure range (in the edematous range) a very minute change in pressure causes a marked change in volume of fluid in the tissues.

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The sudden change in fluid volume of the tissues that occurs when the interstitial fluid pressure rises above atmospheric pressure (above zero) leads to the hypothesis that the resistance to fluid mobility through the tissue spaces should be very high when the interstitial pressure is negative; yet, once the interstitial fluid pressure has risen above the zero level, the sudden onset of edema should greatly expand the interstitial spaces and thereby greatly reduce the resistance to fluid mobility. This study was designed to study changes in resistance to tissue fluid mobility as the interstitial fluid pressure rises from its normal negative value to values above zero.

**Method**

Several different methods were utilized to measure the rate of fluid movement through the tissue spaces, but the one employed most often was that illustrated in figure 1. Two catheters, each 20-cm long, 3 mm o.d., and having approximately 20 1-mm holes distributed along 15 cm of its length, were inserted 17 cm beneath the skin of the abdominal wall in a dog anesthetized with 30 mm per kg of pentobarbital. The catheters were placed 2.5 cm apart and were lodged in the loose connective tissue. Using a long syringe needle, Tyrode's solution was quickly flushed into each catheter to remove the air. The catheters were then connected to the system illustrated in figure 1, with a low pressure Statham transducer connected to each of the catheters, a syringe connected to each, and the two catheters connected to opposite sides of a chamber having a tight membrane in the middle. The entire system was filled with Tyrode's solution containing heparin (30,000 units per L) to prevent clotting of the fluids in the two catheters.

The pressures recorded by the transducers were zeroed to the hydrostatic level of the catheters. Any desired level of pressure could be applied to either catheter by compressing or pulling on the respective syringe. To measure the rate of flow of fluid between the two catheters, a slightly different pressure, 1 or 2 mm Hg, was applied to the two different catheters. This displaced the membrane in the chamber to one side. Because of the pressure difference between the two catheters, fluid began to move from the catheter with higher pressure to the one with lower pressure, and the membrane in the chamber moved back toward the neutral position. When a very compliant membrane was used, a large amount of fluid had to flow from one catheter to the other for a very small pressure change between the two transducers. When a less compliant membrane was used, very minute movement of fluid between the two catheters caused rapid approach of the two pressures toward each other. Each membrane was calibrated so that one could determine the rate of fluid flow between the two catheters from the rate of approach of the two pressures toward each other. Two types of membranes were used, a 0.002-inch thick...
tempered brass membrane and a membrane made of rubber dam. The compliance of the system with the brass membrane was 7 mm$^3$ of fluid per mm Hg pressure differential. Therefore, when the two pressures approached each other at a rate of 1 mm Hg per min the rate of flow between the two catheters was 7 mm$^3$ per min. The system with the rubber membrane had a compliance about 30 times as great as that of the brass membrane; this membrane was used when high flows were to be recorded, such as when the tissues around the catheters were very edematous.

The purpose of using this elaborate procedure for measuring fluid movement through the tissues was to make sure that precisely the same amount of fluid moved out of one catheter and into the other catheter. This eliminated possible errors that could be caused by movement of fluid in the tissue spaces besides that from one catheter to the other.

Other methods utilized in this study were variants of the one illustrated in figure 1. The differences will be pointed out in the presentation of results.

**Results**

**MEASUREMENT OF RESISTANCE AND CONDUCTANCE BETWEEN CATHETERS INSERTED BENEATH THE SKIN**

Figure 2 illustrates results from a typical experiment using the experimental preparation illustrated in figure 1. The pressures in the two catheters were first adjusted to a mean negative value of —5.5 mm Hg with a differential between them of 2 mm Hg, that is, —6.5 mm Hg in one catheter and —4.5 mm Hg in the other catheter. Fluid moved extremely slowly from one catheter to the other, and the two pressures approached each other very gradually over a period of 10 min. From the record of approach and the calibration of the instrument, the resistances and conductances were calculated. Then the same procedure was repeated at a slightly less negative mean interstitial fluid pressure. This process was repeated at many pressure levels between the range of normal negative pressure in the subcutaneous tissues of approximately —6 mm Hg and the edematous level of interstitial fluid pressure at +1 mm Hg. When the mean interstitial fluid pressure in the two catheters approached zero, and especially when this mean value rose into the positive range, only 0.5 mm Hg pressure differential was applied between the two catheters because the rate of fluid flow between the two catheters became much too great for measurement at the higher pressure differentials.

Figure 2 illustrates that the resistance was great in the negative pressure range of interstitial fluid pressure but fell to a value too small to show on the figure when the pressure rose to 0 mm Hg. The plot of conductance in figure 2 illustrates the continued increase in mobility of fluid after the pressure rose above zero.

The same experiment was repeated in nine different dogs, and the results were so nearly identical to those illustrated in figure 2 that the shapes of the curves could be superimposed on each other almost exactly. The upper portion of table 1 summarizes the results from all the experiments, illustrating that when the pressure was increased from the normal negative level up to the positive pressure edematous state, the conductance between the two catheters increased 46,000- to 550,000-fold, averaging 261,000-fold.

It was impossible to calculate the precise volume-resistivity or volume-conductivity of the interstitial fluid.


### TABLE 1

Change in Conductance when the Interstitial Fluid Pressure is Increased from a Negative Value to a Positive Value

<table>
<thead>
<tr>
<th>Expt. No.</th>
<th>Dogs with Catheters</th>
<th>Conductance (cmVdyn/sec cm)</th>
<th>Conductance change (Conductance at +0.6 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At — 5 mm Hg</td>
<td>At + 0.6 mm Hg</td>
<td>(Conductance at +0.6 mm Hg)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>41 x 10^-ii</td>
<td>19 x 10^-5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>69 x 10^-io</td>
<td>47 x 10^-5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>23 X 10^-io</td>
<td>100 X 10^-5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>68 X 10^-io</td>
<td>58 X 10^-5</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>22 X 10^-1^</td>
<td>58 X 10^-5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>24 X 10^-io</td>
<td>132 X 10^-5</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>27 X 10^-io</td>
<td>69 X 10^-5</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>22 X 10^-1^</td>
<td>107 X 10^-5</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>30 X 10^-io</td>
<td>48 X 10^-5</td>
</tr>
<tr>
<td>Average</td>
<td>32 X 10^-io</td>
<td>69 X 10^-5</td>
<td>261,000</td>
</tr>
</tbody>
</table>

| Dogs with Perforated Capsules | 10          | 20 x 10^-9                   | 20 X 10^-5                                  | 10,000                                      |
| Collapsible Tube              | 11          | 125 X 10^-s                  | 86 X 10^-5                                  | 6,800                                       |
| Collapsible Tube & Wool & Gelatin | 12 | 70 X 10^-8                   | 57 X 10^-5                                  | 8,100                                       |
| Perforated Capsules           | 13          | 28 X 10^-6                   | 27 X 10^-5                                  | 9,600                                       |

the tissues, because it was impossible to determine the precise dimensions of the tissue mass through which the fluid moved from one catheter to the other. However, the distance between the two catheters was 2.5 cm, their lengths beneath the skin were 15 cm, and dissection of the tissues after the experiments showed that the depth of the loose connective tissue into which the catheters were inserted—that is, its depth between fascial layers—was approximately 3 mm. From these approximate dimensions and from the average data in table 1, we can calculate that the approximate volume-resistivity of the normal non-edematous connective tissue averaged $56 \times 10^7$ dyne-sec/cm³ per cm³ of tissue. The corresponding volume-conductivity averaged $18 \times 10^{12}$ cm²/dyne-sec per cm³ of tissue. In the edematous state these values changed respectively to $21 \times 10^7$ dyne-sec/cm³ for resistivity and $9.6 \times 10^{-5}$ cm²/dyne-sec for conductivity.

**MEASUREMENT OF RESISTANCES AND CONDUCTANCES BETWEEN PERFORATED CAPSULES IMPLANTED BENEATH THE SKIN**

The same experiment as that illustrated in figure 1 was performed utilizing two implanted perforated capsules instead of catheters. The capsules were surgically implanted 4 weeks prior to use. They were 3.5 cm apart (center to center), and the diameter of each capsule was 15 cm. Each capsule had approximately 100 1-mm holes over its surface. Cells had grown into each of the capsules and had lined the inside of the capsule with fibrous tissue about 3 mm thick. Previous studies had shown that this fibrous tissue is well supplied with vessels and that protein-bound dye (T-1824) placed in the central cavity of the capsule disperses freely through the tissue spaces of the fibrous tissue and thence through the perforations in the capsule into the surrounding tissue spaces.

To measure resistances and conductances between the two perforated capsules, a 20 gauge needle was inserted through the skin to the middle of each capsule, and the needles were connected to the apparatus in figure 1. The experiment was then conducted in the same manner as described above.

Figure 3 illustrates the changes in resistance and conductance as the mean pressure in the...
Measurements of resistance and conductance between two implanted capsules located 3.5 cm apart in the subcutaneous tissue of the abdominal wall. Note that as the mean pressure in the capsules rose toward zero (atmospheric pressure) the resistance fell rapidly almost to zero; the conductance increased precipitously when the mean pressure rose above zero.

Two capsules was increased from approximately —6 mm Hg up to +0.2 mm Hg. Note once again the rapid decrease in resistance as the pressure approached zero and the abrupt increase in conductance that occurred almost precisely at the zero pressure level. The half-time for return of the pressure in the normal state averaged 1.3 ± .4 min, and the capsule pressure averaged —6.4 ± 1.8 mm Hg. Conversely, in the edematous state (average pressure = +3.2 ± 1.5 mm Hg) the half-time of approach was so rapid that we could not measure it accurately, but in all cases it was less than 1 sec. Thus, it is evident that the mobility of the fluid increased markedly between the non-edematous state and the edematous state.

**RESISTANCE TO FLUID FLOW THROUGH COLLAPSIBLE TUBES UNDER CONDITIONS SIMILAR TO THOSE IN THESE EXPERIMENTS**

Many investigators have pointed out the sudden and extreme change in resistance to fluid flow through collapsible tubes when the intraluminal pressure changes from less than atmospheric pressure to greater than atmospheric pressure. To demonstrate the similarity of these previous results to the studies of the present experiment, a 3 ft length of % inch-diameter penrose rubber tubing was used as an experimental model in three different conditions, (a) filled only with water, (b) partially filled with woolen yarn, and (c) partially filled with wool and gelatin. Figure 4 illustrates a typical experiment in which the resistance to water flow through the tube was measured, first when it had no resilient filling, then with more strands of yarn extending the length of the tube. Note that when the tube had no filling, there was a sudden transition from almost infinite resistance to essentially zero resistance when the intraluminal pressure rose above atmospheric pressure. As more strands of yarn were placed in the tube, the transition became more and more gradual. On comparing this figure with figures 2 and 3, one sees that the interstitial spaces have a pressure-flow curve approximately that of a collapsible chamber with a
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Resistance to fluid flow through a 1 cm diameter, 3 ft-long penrose rubber tube at different levels of mean intraluminal pressure in the tube and with different amounts of yarn in the tube. Note that the resistance of the tube having no yarn fell abruptly from almost infinite resistance to almost zero resistance as the mean pressure rose above atmospheric pressure. The presence of the noncollapsible yarn in the tube caused much less precipitous change in resistance.

A small amount of resilient filling material, such as collagen fibers, in the spaces that prevent immediate and sudden collapse.

The experiment in which wool and gelatin were placed in the tube gave almost the same results as those observed without the gelatin. On observing the tube visually during the experiment, it was evident that fluid tended to creep along the wall of the tube outside the gelatin mass, and as soon as the pressure inside the tube rose above atmospheric pressure the tube suddenly swelled so that large channels of free fluid flowed around the gelatin. These experiments were performed because chemical studies have demonstrated that the tissues are filled with a gelatinous 'ground substance' containing large amounts of mucopolysaccharides, mainly hyaluronic acid.

Discussion

SUDDEN CHANGE IN TISSUE FLUID MOBILITY AS THE INTERSTITIAL FLUID PRESSURE CHANGES FROM NEGATIVE TO POSITIVE

The results of this study are mainly self-evident: as the pressure of fluids beneath the skin rises above atmospheric pressure the resistance to movement of fluid through the tissue spaces decreases precipitously.

A question that immediately comes to mind is whether the results were an artifact caused by creation of false channels of fluid flow through the tissue spaces when positive pressure was applied beneath the skin. However, this thought can probably be dispelled by the everyday observance of clinicians that the phenomenon of 'pitting' occurs in extracellular fluid edema. That is, one can press on edematous tissue and easily express fluid out of the tissue. Upon removing the pressure the fluid flows rapidly back into the tissue, and the 'pit' disappears in a few seconds, thus demonstrating free mobility of fluid through the tissue spaces of the edematous person. This phenomenon does not occur in normal tissues even though measurements of interstitial fluid volume (sodium space minus plasma volume) indicate that about 11% of the normal non-edematous body is composed of interstitial fluid.

RELATION OF THE PRESSURE-CONDUCTANCE CURVE OF THE TISSUE SPACES TO THE PRESSURE-VOLUME CURVE

Studies have demonstrated that Poiseuille's equation is applicable to the flow of fluid through channels even as small as the capillary pores. Therefore, it seems reasonable to apply this equation in the present study to approximate the changes in dimensions of the interstitial spaces through which fluid moves when the interstitial pressure rises from a negative to a positive value. Thus Poiseuille's equation:

\[ Q = \frac{TrAPr^4}{8\pi l} \]  

and the equation:

\[ G = \frac{Q}{\Delta P} \]  

can be combined to give a relationship between conductance \( G \) and radius of the flow channels:

\[ G = \frac{77r^4}{8\pi l} \]
And since the volume of a cylindrical channel is:

\[ V = \pi r^2 l \]  

we can combine equations 3 and 4 to give the following relationship between tissue conductance and volume of tissue spaces:

\[ G = \frac{V^2}{8\pi \eta l^3} \]  

And, if we assume that the viscosity of the fluid and lengths of the flow channels remain constant, equation 5 becomes:

\[ V = G^{1/2} \times \text{Constant} \]  

Thus, we see from equation 6 that the volume of the tissue space should change in proportion to the square root of the conductance. In figure 5 the solid curve presents the square root of the conductance curve of figure 2 plotted against interstitial fluid pressure. Thus this curve represents a pressure-volume curve for the mobile fluid of the interstitial spaces as calculated from the data in the present study. By way of comparison, the dashed curve of figure 5 is a measured pressure-volume curve of the interstitial spaces which was reported in one of our previous studies. Both of these curves break suddenly at the zero pressure point, but the break in the curve calculated from the present data is more precipitous than the break in the curve from the previous measurements. The difference probably results from the fact that the calculations above have not taken into consideration other factors such as abnormal geometrical shapes of the tissue spaces, changes in the lengths of the flow channels, and so forth.

**The Concept of Mobile Versus Immobile Extracellular Fluid**

Histological and chemical studies of the interstitial space indicate that it is normally filled with 'ground substance' which is a gelatinous mass of interstitial fluid entrapped in a fine meshwork of polymerized hyaluronic acid and other mucopolysaccharides. Enwined through this gelatinous mass are the collagenous and other types of fibers of the interstitial spaces. Recently, electronmicrographs have demonstrated that the ground substance is not entirely homogeneous but actually has a physical structure with periodically repeating aggregates of electronmicroscopically dense material (Carl Moyer, personal communication). Therefore, one would expect the fluids within the ground substance to have extremely low mobility because they are mainly entrapped in minute interstices within a gelatinous matrix. On re-studying figure 5 one sees that the curves of this figure support this concept for the following reasons: the calculated pressure-volume curve of the mobile fluid indicates that its volume becomes almost zero when the interstitial fluid pressure falls below atmospheric pressure level. On the other hand, the dashed curve of the figure shows that the true interstitial fluid volume is still quite high when the interstitial fluid pressure is negative. This difference could result from the fact that measurements of the interstitial fluid volume as made by measuring the sodium space or some other space depend on diffusion of the test substance into the space, and the process of...
Tissue fluid mobility

diffusion is hindered almost imperceptibly by a gel matrix.

A conclusion of this line of reasoning, if all the facts prove to be correct, is that the interstitial fluid of normal tissues is almost completely immobile, except perhaps for a few small channels of mobile fluid where hyaluronic acid is not present. This same conclusion was indicated by studies of dye movement in tissues by Parsons and McMaster who observed these minute channels of movement. On the other hand, because of the very free mobility of edema fluid, it can be postulated that in edema it is mainly the mobile component of the interstitial fluid that increases in volume rather than the immobile component.

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Interstitial Fluid Pressure: III. Its Effect on Resistance to Tissue Fluid Mobility
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