Measurement of the Interstitial Pressure in Subcutaneous Tissue in Dogs

By Hans Jørgen Ladegaard-Pedersen

ABSTRACT

A probe consisting of a cotton thread fitted inside a 15-cm Teflon tube with an inner diameter of 0.8 mm and connected to a transducer was used to measure the interstitial pressure in the subcutaneous tissue in six anesthetized dogs. The measurements were reproducible with a standard deviation of ±0.64 mm Hg. In six dogs the mean pressure in the subcutaneous tissue of the thorax was —2.74 mm Hg (range —3.25 to —1.99 mm Hg). After hemorrhage and dextran (10%) infusion, the mean pressure decreased by 1.70 mm Hg. After infusion of lactated Ringer’s solution, the pressure increased to the control values.

ADDITIONAL KEY WORDS hemorrhage dextran infusion

The aim of the present study was to measure the interstitial pressure in dogs by a modification of the method described by Scholander et al. (1).

In a review, Landis and Pappenheimer (2) found that most measurements of interstitial pressure performed by inserting a needle into the tissue showed a pressure a few mm Hg above the atmospheric pressure. In 1963 Guyton (3) introduced a method based on pressures in implanted perforated capsules left in situ 4 to 6 weeks before the measurement. The pressure in the capsules implanted in dogs was normally negative, i.e., subatmospheric (around —6 mm Hg), and the intracapsular pressure obeyed Starling’s law of the capillaries. Guyton concluded that this pressure was the correct interstitial pressure. Later, Hopkinson et al. (4) found with the same method a resting value of —2 to —3 mm Hg, which decreased to around —6.5 mm Hg after hemorrhage.

Scholander et al. (1) demonstrated a negative pressure in many plants and reptiles using a “wick” technique similar to that used in the present study. Using the same technique recently, Strømme et al. (5) measured a negative pressure of —3.8 to —6.5 mm Hg in rat, mouse, and guinea pig.

Methods

The Probes.—A cotton thread 6 cm long previously boiled in 0.9% saline was pulled into the end of a polyethylene or Teflon tube 15 cm long (0.9 mm i.d. and 1.1 to 1.23 mm o.d., respectively) leaving 1 cm outside. A three-way stopcock mounted in the other end was directly connected with a Statham SP-37 transducer and an Ellab pressure manometer. For insertion, the probe was fitted within a thin-walled hypodermic needle (17 G), which was inserted subcutaneously and then pulled back, leaving only the tube with the cotton thread under the skin. Before use, the probe and stopcock were boiled in saline for 30 minutes to ensure that the probe was completely free of air bubbles. To prevent bleeding around the probe and clotting of minimal amounts of fibrin in the thread, the cotton thread was dipped in a solution of epinephrine (0.01 mg/ml) and heparin (15 IU/ml) before insertion.

After insertion, the open branch of the stopcock was placed at the same height as the cotton thread. In a probe functioning satisfactorily, a stable pressure is obtained after one half to two minutes. When the skin above the thread was lightly touched, the pressure immediately rose, and returned to a stable value in 1 to 2 minutes, possibly after an undershoot of a few mm Hg.

With properly functioning probes, stable pressures were obtained several times after equilibration of the pressure in the probe with the atmosphere, and after external pressure applied above the catheter tip. One measurement was made in 10 to 15 minutes. The mean of the stable
pressure values was taken as the result of the individual measurements.

**Some Physical Characteristics of the System**

**Compliance of the Probe.**—To determine compliance, the tip of the catheter was closed, and the volume in the probe was varied by 0.05 μl at a time by a special screw arrangement.

**Colloid Osmotic Effect and the Influence of Surface Tension.**—To examine whether a thread could act as a semipermeable membrane and produce a negative pressure as a result of a colloid-osmotic effect, and to examine whether a possible difference in surface tensions between the saline in the probe and the surrounding fluid may influence the pressure recordings, the thread was placed in the following fluids at the same hydrostatic pressure: 0.9% saline, normal plasma, 4 and 22% bovine albumin, lactated Ringer’s solution, 1% albumin in Ringer’s solution, 99% ethanol (a fluid miscible with water, surface tension 29 dynes/cm), and toluene (a fluid immiscible with water, surface tension 29 dynes/cm). Water and diluted electrolyte solutions have surface tensions of 72 to 73 dynes/cm, and plasma has a surface tension of about 50 dynes/cm.

**Measurements in Dogs**

**Significance of the Water Content of the Wick.**—In an anesthetized dog (24 kg), interstitial pressure was measured on the lateral aspects of the thorax. In six measurements, the technique described previously was followed for every other measurement. In the other three measurements, about 4 μl of water was sucked out of the wick. This corresponds to a pressure reduction in the probe from 0 to −1 mm Hg to −7 to −8 mm Hg when the wick is free. The aim was to determine whether the water content of the thread had any influence on the pressure measured. A fresh probe was used for each measurement.

**Normal Interstitial Pressure.**—In five anesthetized dogs this was measured by one or two probes in the subcutaneous tissue on the lateral aspect of the thorax.

Anesthesia was induced by intravenous barbiturate and maintained by nitrous oxide (65%) and halothane in combination with gallamine. A Jefferson respirator was used.

**Interstitial Pressure during Hemorrhage and Forced Diuresis.**—After the control measurements, the following procedures were carried out to reduce the interstitial volume: 10 mg of furosemide was injected intravenously and then the animal was bled for 34 to 63 ml/kg through a catheter in the femoral artery. The blood loss was replaced by intravenous infusion of 19 to 34 ml/kg of a 10% dextran solution (Macrodex).

This procedure was performed over 1 to 2 hours; 30 to 60 minutes later, interstitial pressure was measured two or three times.

**Interstitial Pressure during Rehydration.**—In three dogs, the fluid loss calculated from the hemorrhage, the infusion of dextran solution and the diuresis was replaced by infusion of lactated Ringer’s solution, to give a surplus of around 20 ml/kg. The interstitial pressure was then measured again one to three times.

The blood volume was measured by 131-I labeled albumin in a semiautomatic apparatus (Volémetron [6]).

The blood pressure was continuously recorded through the catheter in the femoral artery using a Statham transducer.

**Results**

**Compliance of the Probe.**—The compliance was found to be approximately 1.5 × 10⁻³ μl/mm Hg.

**Colloid Osmotic Effect and the Influence of Surface Tension.**—The same pressure (within ±0.1 to 0.2 mm Hg) was recorded when the probe was placed in normal plasma, 4 and 22% bovine albumin in Ringer’s solution, and 99% ethanol as when it was placed in saline at the same hydrostatic pressure. When it was placed in toluene the pressure recordings were about 3 mm Hg lower than when placed in saline.

**In-Vivo Measurements**

In experiments on dogs, 93 stable values of pressure were recorded with 29 probes (3.2 pressure values per probe). On pooling the variances, the standard deviation for the stable pressures was ±0.39 mm Hg.

For 11 double determinations, the standard deviation was ±0.64 mm Hg. For the mean value of a double determination, therefore,

\[ ±2 \times se = ±2 \times \frac{0.64}{\sqrt{2}} = ±0.91 \text{ mm Hg} \]

The correlation coefficient between the first and second determination is \( r = 0.81 \) (\( P < 0.001 \)) and the regression equation is

\[ y = 0.98x - 0.007 \]

where \( x \) and \( y \) are the first and second determinations (Fig. 1).

**Significance of Water Content of Wick.**—In the experiment in which interstitial pressure was measured alternately in the usual manner and after removal of about 4 μl of water from
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FIGURE 1

Eleven double determinations. The regression line has been drawn in.

the thread, the values recorded in the first two determinations were $-3.6$ and $-2.1$ mm Hg; in the next two, $-2.1$ and $-2.7$ mm Hg; and in the last two, performed on the other aspect of the thorax 1½ hours after the first two determinations, $-6.6$ and $-5.4$ mm Hg. Thus, in two of the three pairs the pressure was higher in the probe when water was removed from the thread.

Dog Experiments with Hemorrhage and Lactated Ringer's Infusion

In the control period prior to the hemorrhage, interstitial pressure varied in five dogs between $-1.99$ and $-3.25$ mm Hg (mean $-2.61$ mm Hg). After the hemorrhage and dextran infusions, the mean interstitial pressure varied between $-3.17$ and $-5.10$ mm Hg (mean $-4.32$ mm Hg). The decrease is highly significant by the t-test ($P < 0.001$). After infusions of lactated Ringer's solution into three dogs, the pressures were $-1.94$, $-1.89$ and $-2.70$ mm Hg (mean $-2.18$ mm Hg) ($0.01 < P < 0.02$). The results are shown in Figure 2 and Table 1.

After the furosemide injection, the urinary output increased, but nearly stopped after the start of the hemorrhage and dextran infusions. During the infusions of lactated Ringer's solution, the urinary output was still very low until the infused volume was brought up to the lost volume of fluid, when a brisk diuresis started and continued as long as the infusion.

![Figure 2](http://circres.ahajournals.org/content/26/6/767/f2.large.jpg)

**FIGURE 2**

Interstitial pressure in five dogs. C, control measurements; AHD, after hemorrhage and infusion of 10% dextran solution; ALR, after infusion of lactated Ringer's solution.

**TABLE 1**

Interstitial Pressure before and after Hemorrhage and Infusion of 10 Percent Dextran Solution and after Infusion of Lactated Ringer's Solution

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Wt (kg)</th>
<th>Blood vol (ml/kg)</th>
<th>Control IP (mm Hg)</th>
<th>Hemorrhage (ml/kg)</th>
<th>Dextran IP (mm Hg)</th>
<th>Ringer's (ml/kg)</th>
<th>IP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.0</td>
<td>125</td>
<td>-1.99</td>
<td>43</td>
<td>25</td>
<td>-3.17</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>23.6</td>
<td>68</td>
<td>-3.25</td>
<td>29</td>
<td>21</td>
<td>-5.10</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20.0</td>
<td>73</td>
<td>-2.57</td>
<td>56</td>
<td>30</td>
<td>-4.59</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>17.5</td>
<td>73</td>
<td>-2.65</td>
<td>63</td>
<td>34</td>
<td>-4.08</td>
<td>114</td>
</tr>
<tr>
<td>5</td>
<td>21.0</td>
<td>98</td>
<td>-2.60</td>
<td>34</td>
<td>19</td>
<td>-4.65</td>
<td>76</td>
</tr>
<tr>
<td>Mean</td>
<td>20.4</td>
<td>87</td>
<td>-2.61</td>
<td>45</td>
<td>26</td>
<td>-4.32</td>
<td>93</td>
</tr>
</tbody>
</table>

IP = interstitial pressure.

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In dog 2, there was a brief fall in blood pressure during the hemorrhage. In the other dogs there were only small changes in blood pressure.

**Discussion**

In all six dogs, the control measurements were negative (mean $-2.65$ mm Hg, SD ± 0.46) and corresponded to the "capsule pressures" found by Hopkinson et al. (4) (mean $-2.75$, $\text{sn} \pm 0.35$ mm Hg) and the 2- to 4-week values found by Guyton (3) (mean $-2.5$ and $-2.8$, $\text{sn} \pm 0.7$ to $-1.8$ mm Hg depending on localization), but were higher than Guyton's "more than 4-week" values (mean $-5.5$ to $7.1$, $\text{sn} \pm 1.3$ to $2.8$ mm Hg).

After increasing the urinary output by furosemide, hemorrhage, and part substitution of the lost blood by infusion of dextran (10%), the interstitial volume is reduced, and a decrease of interstitial pressure should be expected. The mean decrease of 1.71 mm Hg is highly significant ($P < 0.001$).

Conversely, it should be expected that the pressure would rise after infusion of lactated Ringer's solutions, and the mean increase of 2.14 mm Hg in the three experiments performed is significant ($0.01 < P < 0.02$). The final values were of the same order of magnitude as the control values. The brisk diuresis obtained seems proof of a normally hydrated dog after the infusion of lactated Ringer's solution.

None of the five experiments failed to demonstrate a change in the measured pressures in the expected direction, and the measured pressure was of the same order of magnitude as that in implanted capsules.

In the double measurements the correlation was high, the regression coefficient being 0.98.

Although the results obtained thus appear to be acceptable, there are nevertheless several sources of error. Tissue damage, with edema and hemorrhage around the tip of the catheter, may result in too high values. Severe hemorrhage is noticed immediately by a steeply rising pressure curve. Bleeding in the form of small red spots on the cotton thread does not seem to affect the result. The addition of epinephrine to the thread reduces the tendency to bleeding and may also be presumed to reduce the formation of edema. Simultaneously, the factors changing the local interstitial pressure, i.e., the forces changing the interstitial volume, diminish. This means that the recorded pressure will be the pressure at the time of insertion, and that it will reflect pressure changes in the surrounding tissue only to a slight degree during the measurement.

Another source of error is the amount of water exchanged between the thread and the tissue before the pressure in the probe is in equilibrium with the pressure in the tissue. When about 4 $\mu$l of saline was removed before insertion, there were no significant deviations from the pressures recorded in the usual way.

None of the errors will give reduced values for the pressure. Furthermore, the volume of the wick itself inserted into a minute tissue space could itself increase the pressure and make it more positive than it otherwise would have been. This possibly explains why the pressures recorded were less negative than those recorded by Guyton in his capsules 3 to 4 weeks after implantation. In favor of the method is that it is easy to use, the contact area with the tissue spaces is great, and infusion of fluid during the measurement is not necessary.

As found by Strømme et al. (5), the negative pressure cannot be explained by a colloid osmotic effect. When the probe is placed in different protein solutions, the same pressure is obtained as when it is in saline with the same hydrostatic pressure.

The surface tension of the interstitial fluid is unknown, and it is impossible to obtain fluid that is unquestionably interstitial fluid. But it seems reasonable to suppose that the surface tension of interstitial fluid will not differ significantly from the surface tension of the fluids tested in this work, which did not influence the pressure recordings. With an unphysiologic fluid like toluene, which does not mix with, and has a surface tension far
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different from, the saline, a significant influence was registered.

The method is applicable to human subjects—normals and patients—and preliminary measurements have been performed in 20 normally hydrated persons (unpublished data). The range was —2.4 to +2.81 mm Hg, mean —0.63 mm Hg. The higher pressures may be due to the species difference. The same standard deviation and high correlation between the double determinations are found in human subjects.

The negative pressures recorded in dogs by the present method are in accord with the pressures recorded by Guyton (3) and Hopkinson et al. (4). The experiments performed by Guyton seem to be very convincing, but nevertheless the possibility of a negative interstitial pressure has been exposed to some criticism (7-9).

Wiederhielm (9) found that the negative pressure in implanted capsules may result from development of a semipermeable membrane. This is not a possibility in the present series.

Against the concept of a negative pressure, McDonald (7) has argued that the intercellular space in a horizontally positioned body must be in equilibrium with the atmosphere, and in the gut, for instance, is in direct communication with the atmosphere. This, he feels, makes it difficult to accept reports of a negative interstitial fluid. This argument is hardly tenable if the possible role of capillarity is considered. Where the interstitial space is in direct communication with the atmosphere—naturally or accidentally—the capillary effect of the very minute tissue spaces may prevent the negative pressure from pulling air into the interstitial space.

It can be difficult to accept the concept of a negative pressure in the intercellular space if one imagines a space filled with water. The pressure would be transmitted freely to the venules, for example, which would therefore be constantly dilated if the surrounding pressure was negative. On the basis of indirect measurements of venous pressure, Kjellmer (8) found that the surrounding pressure must be slightly above zero. But as suggested by Guyton (10), the surrounding pressure is not only the interstitial fluid pressure but also a solid tissue pressure. These “compressional forces of the solid and semi-solid elements of the tissues” together with the fluid pressure form the total tissue pressure. It is this pressure which acts on the capillaries and venules and is recorded from a balloon placed in the tissue. As mentioned by Guyton, the needle pressure is the pressure necessary to displace the tissue when small amounts of fluid are infused, i.e., the total tissue pressure.

Studies on the intercellular substance in connective tissue are in accord with the possibility of a negative fluid pressure in the interstitial space. A well-known characteristic function of the ground substance is its ability to swell when it is placed in saline. When it does not swell in vivo, a probable reason is a negative interstitial fluid pressure.

The apparently contradictory results of measuring the interstitial pressure, where measurements of venous pressure and measurements with a hypodermic needle usually but not always (11) give slightly positive values and measurements with capsule or cotton thread give negative values, can thus be explained by the above assumption.

References


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