Interstitial Fluid Pressure

V. NEGATIVE PRESSURE IN THE LUNGS

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ABSTRACT

Interstitial fluid pressures in the lung were estimated in 39 dogs from pressure measurements made in implanted perforated capsules. Special operative procedures were used to minimize operative trauma of the lungs and infection and inflammation in and around the implanted capsules. In 86% of the preparations, the x-ray findings indicated little remaining inflammation and edema around the capsules, though autopsy findings indicated that a few of these did still have some edema not detectable by x-rays. In 29 of 34 animals in which x-ray findings indicated no edema, the intracapsular pressure was negative. The average of the measurements in all 34 animals was —5.8 mm Hg (± 0.8 SEM), and in the 29 animals with negative pressure values the average was —7.3 mm Hg (± 0.6 SEM). In eight capsules the pressures were below —10 mm Hg, ranging to —16 mm Hg. Because the tissues around some of the capsules undoubtedly still had varying degrees of inflammation and edema, despite the failure of roentgenograms to show these, it is suggested that the normal interstitial fluid pressure of pulmonary tissues in dogs is somewhat more negative than the capsule pressure measurements indicate, perhaps as low as —10 mm Hg.

ADDITIONAL KEY WORDS

pulmonary edema tissue fluids

capillary membrane interstitial fluid body fluids lungs
tissue pressure dogs

In several studies, the interstitial fluid pressures of various tissues were investigated by implanting perforated hollow plastic capsules in the tissues and then measuring the pressures in the cavities of these capsules after complete healing (1-3). With this method, negative fluid pressures were registered in subcutaneous tissue, muscle tissue, retroperitoneal tissue, and the scrotum. On the other hand, attempts to measure pressures by this procedure in the lung, both in our laboratory and in others, had heretofore given nothing but positive pressures. However, we had never been able to eliminate the complication of inflammation in the lung parenchyma around the implanted capsules. In all our previous studies in tissues other than the lung (1) we had found that inflammation is always accompanied by localized edema and that the measured pressures in the implanted capsules are always positive under these conditions. Therefore, the positive pressures heretofore measured in capsules in lungs were exactly what would have been expected because of the persisting inflammation. Still, on the basis of the accepted low normal capillary pressures in the lungs compared with the relatively high capillary pressures in peripheral tissues, the pressure in the interstitial fluid spaces of the lungs can be calculated to be even more negative than the —6 to —7 mm Hg measured in most peripheral tissues of the body.

Circulation Research, Vol. XXII, February 1968 263
In the present studies, special efforts were made to eliminate infectious and inflammatory processes around the implanted capsules in the lung. Special care was exercised in the operative procedure itself, and, even more important, intensive antibiotic therapy was given.

**Methods**

Three kinds of capsules were used: (a) a cellulose acetate hollow sphere with a diameter of 2 cm and perforated by about 200 1-mm holes, (b) one-half of the above sphere (a hemisphere closed by a flat surface on one side), and (c) a plexiglass hollow sphere with a diameter of 1.8 cm and perforated by approximately 150 holes. No difference could be discerned in the results from the different types of capsules. A polyvinyl tube 50 cm long with an inside diameter of 1.5 mm was cemented to each of these perforated capsules so that the attached end of the tube protruded inward to the center of the cavity of the capsule.

The capsule was implanted in the caudal lobe of the left lung. To do this, a cleavage plane was opened on the surface of the lung along one of the interlobular septa, mainly by blunt dissection. On approaching the center of the lung the cleavage plane always played out, and a final incision to approximately the middle of the lobe was accomplished by sharp dissection. As many of the sectioned vessels and minute bronchi as possible were tied off. After the capsule was put in place at the bottom of the incision, the incision was closed with interrupted sutures. Some of the sutures were placed very close to the buried capsule to keep it from moving away from its implanted position, and others were placed in the cleavage plane all the way to the surface of the lung. After implantation was completed, the lungs were overinflated to ensure that the caudal lobe was well aerated and that the implanted capsule was surrounded by functioning lung tissue.

The free end of the tube attached to the capsule was passed through the sixth intercostal space to the exterior at a point approximately 4 inches from the midline of the back, a point where the end of the tube was mainly inaccessible to the dog's paws. The free end of the tube was stoppered with a brass adapter perforated by a hole. The adapter, in turn, was covered with an airtight rubber cap. The capsule and tube were filled with a solution containing 50,000 units of crystalline penicillin/ml before placing the rubber cap over the adapter.

During the first two weeks, the dogs received daily injections of penicillin (400,000 units) and streptomycin (0.5 g); during the second two weeks, antibiotic therapy was given on alternate days, and thereafter twice weekly.

The pressure inside the capsule was measured by inserting a 22-gauge syringe needle through the rubber cap and brass adapter into the lumen of the tube. The needle was connected to a polyvinyl tube 1.0 mm i.d. and 100 cm long. The other end of this tube was connected to a Statham low-pressure transducer that was connected to a Varian recorder or to a Grass polygraph. The tube and needle were filled with isotonic saline or saline containing 1 part zephiran chloride in 1,000 parts. The type of fluid made no discernible difference in the measured pressure. All these procedures were accomplished using sterile precautions.

The zero reference point for each pressure measurement was atmospheric pressure at the midlevel of the respective capsule. The midlevel of the capsule was determined by fluoroscopy. The coordinates of the capsules in the lung were approximately as follows: anteroposteriorly, the capsule was located approximately halfway between the anterior and posterior margin of the left lung. Longitudinally, the capsule was located opposite the upper third of the heart. Transversely, the capsule was located almost exactly in the middle of the left lung, midway between the mediastinum and the lateral margin of the lung. To establish the zero pressure level on the recording, the transducer was connected to a water manometer whose meniscus had previously been adjusted to the midlevel of the capsule (1).

Thirty-nine dogs were used in this study. Roentgenograms were made periodically to assess the degree of inflammation and pulmonary consolidation around the capsules.

**Results**

During the first 2 to 4 weeks after the capsules were implanted, the intracapsular pressures were 0 to 5 mm Hg positive with respect to atmospheric pressure at the same hydrostatic level as that of the capsule. This has also been the experience with capsules implanted in other tissues of the body; extensive studies have shown that positive pressures always occur during the edematous stage of the early postoperative recovery process (1). X-ray studies at this same time showed abnormal density around the implanted capsules, presumably indicative of exudation around the capsules. Autopsies on dogs that were killed during this period also showed exudation around the capsule.
Three to four weeks after the capsules were implanted, x-ray studies showed almost complete recession of the density around the capsules in 34 of the 39 animals. In the other 5 animals, varying degrees of increased density were still apparent.

In six of eight animals killed between the fourth and eighth weeks, the interior surface of the capsules was lined by a thin layer of connective tissue similar to that previously observed in capsules implanted in subcutaneous tissue (1). In the other two animals, the capsules had not formed an internal lining. However, in animals killed 9 to 18 weeks after capsule implantation, some of the capsules were almost completely filled with fibrous tissue, as in capsules implanted in other tissues.

In essence, therefore, capsules implanted in the lungs undergo the same stages of tissue reaction (the tissue lining of the capsules and finally consolidation of the capsules) as has been found in subcutaneous, muscle, and retroperitoneal tissues (1). Also, from these studies the time that appeared to be most nearly ideal for estimation of interstitial fluid pressure from the pressure in the capsule was approximately 4 to 8 weeks after implantation, because during this time most of the postoperative edema had receded and the capsules had not yet undergone consolidation.

When a capsule is implanted in a lung, it is possible to prove the presence of edema only if it is very severe; moderate degrees of edema, which might still be enough to cause positive intracapsular pressure, can easily go undetected except in the few animals killed for autopsy. Therefore, we had to assume that a few of the animals in which x-ray findings were normal still had some degree of inflammatory edema around the capsules even between the fourth and the eighth weeks, and we could not be sure in which animals this was true.

**INTRAUTERINE PRESSURE FOUR TO EIGHT WEEKS AFTER IMPLANTATION**

Between 4 and 8 weeks after implantation, a total of 52 pressure measurements were made in 39 animals; 41 of the measurements gave negative pressures, and 11, positive pressures. (These results, however, include seven measurements made in five animals with definite x-ray evidence of consolidation around the capsules, as will be explained below.) The average of all 52 measurements was $-4.7 \text{ mm Hg} \pm 0.9 \text{ mm Hg (SEM)}$. To test the significance of these measurements, we calculated the probability that the true mean value of the intracapsular pressure is positive rather than negative. The $P$ value for this was $3 \times 10^{-7}$, which indicates that there is almost infinitesimal probability that the true mean value of intracapsular pressure is positive rather than negative.

Because infection frequently occurred after repeated measurement of pressure in the capsules, no more than two measurements were made in any single capsule during the 4 to 8 weeks. Such measurements were made 2 or 3 weeks apart in 13 dogs. Three were positive and ten were negative at the initial measurement. When measured again, the pressure change in any given capsule averaged less than 2 mm Hg. None of the negative capsules became positive, and of the three positive capsules two remained positive and the other fell from $+1 \text{ mm Hg}$ to $0 \text{ mm Hg}$.

X-ray studies in the 39 animals during the same 4 to 8 weeks showed increased density around the capsules in five of the animals. Seven pressure measurements were made in these animals; six were positive and one was negative, and the average of all seven was $1.4 \text{ mm Hg}$.

If only the results from the 34 capsules without x-ray signs of increased density are considered, the pressure measurements were negative in 39 of 45 measurements and in 29 of 34 of the animals. The average pressure

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1The method for making this calculation is the following (4): A standard distribution curve is constructed mathematically around the mean value, using the standard error of the mean to determine the spread of the curve. Using a standard $T$ table, the fraction of the total area under the curve that is on the positive side of 0 mm Hg is then determined to calculate the probability. In the above calculation, this fractional area was $3 \times 10^{-7}$. 

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The pressure became very erratic after 9 weeks, just as it does in capsules implanted in other tissues of the body (1). Upon removal of capsules from the lungs, there were several abnormalities in the capsule implants which could have accounted for the erratic pressure measurements. First, many of the capsules by this time had become filled with fibrous tissue so that the pressure measurements themselves were no longer valid. Second, following earlier measurements of pressure from the capsules, injection accompanied by edema developed around some capsules despite antibiotic therapy. Third, in more than half the capsules from animals killed during this period, fibrous tissue had grown over the tip of the catheter, and movement of fluid into or out of the catheter was either entirely or partially obstructed, making pressure measurements totally unreliable.

Despite the unreliability of the pressure measurements, the pressures were still negative in 16 of 27 surviving animals during the ninth to twelfth weeks. During the thirteenth to eighteenth weeks, the pressures generally became more positive; at the time of death 9 of the 27 animals still had negative pressures and 18 had positive pressures. Ten animals had been taken off antibiotic therapy 4 weeks before they were killed. All 10 animals developed positive pressures that averaged +5 mm Hg by the time of death. If we exclude these 10 animals from the above figures, 9 still had negative pressures and 8 had positive pressures at the time of death.

In essence, the measurements in animals more than 9 weeks after implantation of the capsules were fraught with too many difficulties for these measurements to be meaningful.

**EFFECT OF VARIOUS CONDITIONS ON THE CAPSULE PRESSURE**

**Respiration.**—The pressure in the capsule fluctuated considerably during the different phases of the respiratory cycle. During normal quiet inspiration the pressure decreased to as low as 8 mm Hg below the mean level. During quiet expiration the pressure rose 1 to 2 mm Hg above the mean level. Thus, the effect of expiration on capsule pressure was usually insignificant compared with that of inspiration (Fig. 1). During tachypnea, the pressure deviated only slightly from the mean level obtained between respiratory cycles. Forced inspiration produced a drop of 20 mm Hg or more in the capsule pressure.

**Posture.**—The mean capsule pressure was 1 to 3 mm Hg more negative in a standing animal than in an animal lying on its right side (that is, with the capsule in the upper lung), averaging 1.3 mm Hg more negative in 10 comparative measurements.

**Positive Pressure Breathing and Negative Pressure Breathing.**—Positive or negative pressure breathing was produced by slipping a mask over the snout of the animal and applying either pressure or vacuum to the mask for periods of 1 to 20 minutes. The pressure in the mask and its effect on the pressure in the capsule was registered on a Varian recorder or Grass polygraph (Fig. 2).
Effect on capsule pressure caused by positive pressure breathing. This record shows approximately half as much increase in capsule pressure as in mask pressure.

Pressure changes in the capsule and mask were in the same direction, but the intracapsular pressure was still changing at the end of each of the periods of positive or negative pressure breathing, indicating that an equilibrium pressure was never reached. When atmospheric pressure breathing was resumed, the pressure in the capsule took from 1 to 5 minutes (average 2.5 minutes) to return to its original value. Similar results were recorded in 7 animals.

Addition or Subtraction of Fluid in the Capsule.—When 1 to 4 μliters of fluid was injected rapidly into the capsule, the pressure immediately rose an average of 4 mm Hg per μliter of injected fluid, as illustrated in Figure 3, but it returned almost to the baseline within 10 to 60 seconds. If the fluid was injected more slowly, more had to be injected to effect a change in pressure. Removal of fluid affected the capsule pressure similarly but in the opposite direction.

Intravenous Infusion of Tyrode’s Solution.—Tyrode’s solution was infused intravenously at an average rate of 1 liter/11 minutes in 6 dogs weighing 18 to 29 kg. One animal died after 4 liters of fluid was administered, two accommodated as much as 7 liters, and three, 11 liters. As the infusion progressed, the capsule pressure (Fig. 4) increased an average of 2 mm Hg/liter of fluid infused.

Elevated Left Atrial Pressure.—In three dogs the chest was opened, and a catheter was inserted into the left atrium by way of the auricular appendage to measure left atrial pressure. Also, a specially designed screw clamp with a long stem was placed around the aorta. Following insertion of the catheter into the auricular appendage and application of the screw clamp, the catheter and stem of the clamp were brought to the outside of the chest through the operative wound, and the chest was closed. The left atrial pressure
FIGURE 5

Effect on capsule pressure caused by elevation of left atrial pressure.

could then be elevated to any desired level by tightening the clamp to cause left ventricular failure.

When the left atrial pressure was elevated above normal, the capsule pressure began to rise immediately. Figure 5 illustrates typical results from one of the three experiments in which the left atrial pressure was first elevated to 17 mm Hg for 20 minutes and then further elevated to 35 mm Hg for an additional 52 minutes. Note that the normal capsule pressure was −8 mm Hg. An immediate increase in left atrial pressure to 17 mm Hg caused an instantaneous rise in capsule pressure of 2 mm Hg, which is the same effect that has been observed previously for capsules implanted in peripheral tissues when the venous pressure is elevated (3). The pressure then continued to rise slowly for the next 10 minutes, when it reached a plateau. After 10 minutes on this plateau, the left atrial pressure was elevated to 35 mm Hg. For the next 52 minutes, fluid continued to transude into the tissues, and no new plateau was ever reached. Instead, the intracapsular pressure rose progressively above the zero level, reaching +3 mm Hg. During the latter phase of the experiment gross bubbling râles were heard in the chest.

Discussion

This study was undertaken to determine whether the pressure in the interstitial spaces of the lungs is negative under normal conditions, as would be predicted from the Starling concept of equilibrium of forces at the capillary membrane (5). If we assume that such an equilibrium does apply to the pulmonary capillaries, then we can calculate the theoretical level of pulmonary interstitial fluid pressure. The approximate normal colloid osmotic pressure in dog plasma is about 22 mm Hg (6); in interstitial fluid, as estimated from pulmonary lymph protein concentration (7), it is about 5 mm Hg. Finally, pulmonary capillary pressure has been measured by the isogravimetric procedure to be about 7 mm Hg at the midlevel of the isolated lung (8). For an equilibrium state to exist at the pulmonary capillary membrane, interstitial fluid pressure at approximately the level of the heart should equal pulmonary capillary pressure plus colloid osmotic pressure in interstitial fluid minus colloid pressure in plasma, or 7 mm Hg + 5 mm Hg − 22 mm Hg = −10 mm Hg.

If Starling’s concept of equilibrium at the capillary membrane applies to the pulmonary capillary membrane, and if the capsule method for measuring interstitial fluid pressure is as valid in the lungs as it appears to be in other tissues, the pressures measured in perforated capsules implanted in dog lungs at the level of the heart should record values for interstitial fluid pressure of approximately −10 mm Hg.

In the animals studied in the present experiments, in 86 of which intensive antibiotic therapy eliminated infection and inflammation of the lungs (as determined by x-ray studies), the average intracapsular pressure was −5.8 mm Hg. However, there is reason to believe that the true interstitial fluid pressure of the lungs is even more negative than this value, because there was always the possibility that some inflammation and edema persisted around the implanted capsules that was not revealed by x-ray studies.

Thus, the net result of all of our experience with implanted capsules in the lungs may be
PULMONARY INTERSTITIAL FLUID PRESSURE

summarized as follows. Whenever it has been possible to eliminate infection and inflammation around the implanted capsules, almost all the measured pressures in the capsules have become negative. Yet, with the slightest lack of diligence in maintaining antibiotic therapy, the pressures have become positive.

The results of all these studies, however, must be qualified by two additional considerations: the source of the blood vessels that grow into the tissue surrounding the capsules and the effect of gravity on the interstitial fluid pressure. The tissue that grows around the capsule and also penetrates the holes to line the interior of the capsule is typical connective tissue. Though it is questionable whether the blood supply to this connective tissue is derived from the pulmonary vessels or the bronchial vessels, it is our belief that most of it is pulmonary in origin, for the following reasons. In order to plant the capsules in the middle of the lung lobe, it is always necessary to cut into actual lung parenchyma at the depth of the incision. Therefore, it is certain that the capsules were initially implanted in areas supplied mainly by pulmonary vessels. Furthermore, autopsy showed functioning alveoli within 2 mm of the capsules on most of their sides (whenever infection and inflammation were not present). Obviously, if a major share of the vasculature to the capsules were derived from bronchial vessels, in which the capillary pressure is presumably much higher than it is in pulmonary vessels, one would expect much less negative interstitial pressure than if all the vasculature were pulmonary. This could have accounted, at least partially, for our failure to show pressures in many of the capsules as negative as one calculates by use of the Starling equation for equilibrium at the pulmonary capillary membrane.

Because of the low level of pulmonary vascular pressure, gravitational (or hydrostatic) factors are almost as important in determining the pulmonary capillary pressure as are the hydrodynamics of blood flow in the lungs. Therefore it is expected that the pulmonary capillary pressures in the lower reaches of lungs are much higher than the mean value of 6 to 8 mm Hg generally quoted for pulmonary capillary pressure at the level of the heart, and the pressures in the upper reaches of the lung should be somewhat lower. For this reason, it is likely that there is a range of pulmonary interstitial fluid pressures, which become progressively more positive at lower levels in the lung. Yet, if we are correct in believing that the interstitial fluid pressure at the level of the heart is as negative as —10 mm Hg, then there should be a considerable safety factor against the development of positive pressure (and edema) in the interstitial fluid spaces even at the lowest level of the lungs. For instance, at a hydrostatic level 13 cm below the level of the heart, the lung tissues should still barely be able to maintain a negative interstitial fluid pressure. Furthermore, if the increased intracapillary pressure in the lower parts of the lungs dilates the capillaries and veins, thereby eliminating most capillary and venous resistance, it is possible that the animal could maintain a negative interstitial fluid pressure in lung tissue located as much as 15 to 20 cm below the mean level of the heart.

The dynamic studies made during the course of these experiments, such as the measurements of pressure changes (a) following injection of fluid into a capsule, (b) following the creation of generalized edema by infusion of Tyrode’s solution into the animal, and (c) following the creation of pulmonary edema by elevating left atrial pressure, were performed mainly to demonstrate that the intracapsular pressure changes in the direction that would be expected from the concept of Starling’s equilibrium at the capillary membrane. These studies showed that several factors that are known to cause edema in the lungs also increase the pressure in the capsule from its usual negative value up toward the zero pressure level or beyond zero into the positive pressure range. These effects are entirely comparable to those that have been found in peripheral tissues of the body in previous studies (1-3). Also, the
rapidity with which capsule pressure re-equili-brates after introduction of or removal of a few microliters of fluid from the capsule demonstrates that the fluid within this cavity is not encysted but is in dynamic equilib-rium with fluids outside the capsule.

The pressure changes during the course of respiration occurred extremely rapidly, indeed much too rapidly for the pressure inside the capsule to have come to equilibrium with the pressure of the fluid in the surrounding tissue spaces. Therefore, these pressure changes were undoubtedly caused partly, if not almost entirely, by pressure exerted on the outside of the capsule by the solid tissues surrounding the capsule rather than by pressure changes in the fluid of the interstitial fluid spaces. This is one of the artifacts of the capsule method for measuring interstitial fluid pressure, and it has been noted previously in relation to pressure measurements in interstitial fluid spaces of peripheral tis-sues (1). The basic theory of the capsule technique is to provide a perforated structure that has enough solidity to be mainly non-compliant. Unfortunately, it is impossible to make a capsule absolutely noncompliant. Therefore, solid pressure applied to the tissues surrounding the capsule can cause protrusion of tissues inward through the perforations into the capsule and produce a momentary elevation of the pressure within the capsule. For instance in studies using capsules located in subcutaneous tissues, one can press a finger tightly against the capsule and raise the pressure in the capsule suddenly as much as 20 mm Hg. However, if he holds his finger on the capsule for 2 to 3 minutes with the same degree of applied force, the pressure inside the capsule returns almost to the original normal negative pressure value. Upon removal of the finger, the pressure now becomes 20 mm Hg too negative, and it re-adjusts over a period of the next few minutes back to its original mean value. Thus, capsule pressure can be affected momentarily by solid force applied to the outside of the capsule. In the lungs, respiratory movements can cause solid forces to be imposed on the capsule by the lung tissues. For this reason, there is no logical way to analyze the significance of the second-by-second respiratory excursions in the capsule pressure. However, this in no way detracts from the applicability of the capsule method for measuring changes in mean interstitial fluid pressure that occur over a period of many minutes.

These studies on negative interstitial fluid pressure in the lungs corroborate the studies of Agostoni on the absorptive capability of the visceral pleura of the lungs (9). Agostoni found that the visceral pleura is capable of absorbing fluid against negative pressures down to $-8$ mm Hg in the open chest (calculated to be about $-12$ mm Hg in the closed chest). He assumed that this was caused by the same imbalances of pulmonary capillary pressure and colloid osmotic forces as those discussed above. It is especially noteworthy that the range of negative pressure in Ago-stoni's experiments was very similar to the range of negative pressures in the present experiments.

In conclusion, these experiments support the idea that Starling's concept of equilibrium at the capillary membrane does apply for the pulmonary capillary membrane equally as well as it does for other capillary membranes in the body. They also indicate that interstitial fluid pressure as calculated from the Starling equilibrium equation, a calculated value of about $-10$ mm Hg, is not an unreasonable approximation of the true pulmonary interstitial fluid pressure at the level of the heart.

In the human being, in whose plasma the colloid osmotic pressure is about 6 mm Hg greater than it is in the dog, one would cal-culate from this same equation that the normal human interstitial fluid pressure at the level of the heart would be about $-16$ mm Hg. Such a negative pressure could be very important in keeping the interstitial spaces of the lung in a collapsed state and thereby in helping to maintain relative dryness of the lung tissues. This negative pressure could also play a role in absorption of fluid from the alveoli.
PULMONARY INTERSTITIAL FLUID PRESSURE

References
Interstitial Fluid Pressure

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