Pressures in static and dynamic states from capsules implanted in the kidney

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OTT, C. E., L. G. NAVAR, AND A. C. GUYTON. Pressures in static and dynamic states from capsules implanted in the kidney. Am. J. Physiol. 221(2): 394-400. 1971.—Renal interstitial fluid pressure was measured in 35 unanesthetized dogs from perforated capsules implanted in the kidney. Pressure measurements were made from a small catheter run from the interior of the capsule to the exterior of the animal. Measurements were made approximately every 3 days for a period of up to 60 days. The average pressure obtained in over 150 measurements was 6.0 ± 0.52 mm Hg (SEM). These results indicate that the renal interstitial fluid pressure is lower than previously suggested by other methods. Acute experiments were performed in 24 animals in which a) renal arterial pressure was altered, b) renal venous pressure was increased, c) ureteral pressure was increased, or d) 1.0 M mannitol was infused. The renal interstitial fluid pressure changed in response to all of the above stimuli. The effects on the renal interstitial fluid pressure caused by ureteral pressure or venous pressure changes were over 10 times as great as those caused by a similar change in arterial pressure. The possibility is discussed that changes in renal arterial pressure, renal venous pressure, and ureteral pressure, as well as infusion of osmotic diuretics, can affect the overall balance of forces across the tubular wall in part through their effects on renal interstitial fluid pressure.

First, there is the interstitial fluid pressure which is the pressure exerted by the fluid in the interstitial spaces. This is the pressure responsible for fluid movement. Second, there is the solid tissue pressure which is the pressure exerted by the solid and semisolid elements at their points of contact. This is the pressure responsible for deformation of tissues. Third, there is the total tissue pressure which is an algebraic sum of the interstitial fluid pressure plus the solid tissue pressure acting on a surface area. This is the pressure that tends to displace membranes, such as to collapse blood vessels or tubules. Since the solid tissue pressure is exerted only where the solid elements are in contact and the fluid pressure is exerted only where the fluid is in contact with a surface, the relationship between interstitial fluid pressure, solid tissue pressure, and total tissue pressure can be represented by the following (17):

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\text{total tissue pressure at any area} = (\text{solid tissue pressure}) \times (\text{portion of area over which solid pressure is exerted}) + (\text{interstitial fluid pressure}) \times (\text{portion of area over which fluid pressure is exerted})
\]

From the above relationship it can be seen that if the interstitial fluid pressure increases and the solid elements are pushed apart, then the total tissue pressure will approach the interstitial fluid pressure because the area of contact between the solid elements will approach zero. On the other hand, if the fluid pressure is decreased or goes negative, then the solid elements are pulled together more closely and the solid tissue pressure will increase. It can also be seen from the above relationship that any attempt to measure interstitial fluid pressure which allows solid tissue pressure to be a factor will yield a value which is too high because the interstitial fluid pressure and the solid tissue pressure are additive. These relationships are discussed at length in other publications (14, 17).

In order to eliminate the effect of the solid tissue pressure on the measurement of the renal interstitial fluid pressure, the implanted capsule technique previously developed and tested in other parts of the body (8, 13, 15, 16, 18, 19, 26) was slightly modified for this study. Implanted capsule pressures were measured in chronic unanesthetized dogs and also in acute experiments. The mean pressure obtained in this series of experiments was 6 mm Hg. Furthermore, the capsule pressure increased in response to increases in renal arterial pressure, renal venous pressure, and ureteral...
pressure, and it also increased upon infusion of mannitol solutions.

**METHODS AND MATERIALS**

The basic technique and theory of the capsule method for measurement of interstitial fluid pressure have been discussed previously in detail (15, 16, 18, 19, 26). However, several modifications were necessary for use of the capsule in a small and highly vascular organ such as the kidney. Polyvinyl capsules 12 X 8 mm in size and ellipsoidal in shape were attached to no. 20 gauge vinyl tubes approximately 30 cm long. Approximately 100 small holes were made in the capsules with a hot 26-gauge needle. In order to minimize any reaction with the tissue and to prevent clotting in the tube, the capsules and tubes were coated with a silicone solution (Dow Corning Z-4141 dispersion).

Because of their small size the capsules tended to become filled with tissue after a shorter than normal time. It was therefore necessary to implant two capsules in each kidney so that at least one satisfactory capsule would be available for the acute portion of the experiment.

Mongrel dogs weighing between 10 and 19 kg anesthetized with 30 mg/kg sodium pentobarbital were used. A capsule was implanted in the substance of the cortex of the cranial and caudal pole of the left kidney of each animal through a midline incision. After implantation, each capsule and tube was flushed with sterile saline or water, and the tubes were sealed. The renal capsule was then repaired using a tissue adhesive (Ethicon M2C-2 methyl 2-cyanoacrylate). The tubes from the perforated capsules were routed to the exterior of the animal, either through the midline incision or through the left side of the animal. The animal was placed in a protective jacket to prevent infection. Following surgery, they were placed on 250 mg/day ampicillin to prevent infection.

Following recovery, the animals were trained to lie on a table, and pressure measurements were made under unanesthetized conditions approximately every 3 days for as long as 80 days. A 26-gauge needle connected to a low-pressure Statham transducer and a Coleman microtracer were utilized with results recorded on a Grass polygraph recorder. The recorder was zeroed by placing the needle in a beaker of tissue saline and to prevent clotting in the tube, the capsules and tubes were coated with a silicone solution.

The acute experiments were performed between 20 and 80 days following capsule implantation. The animal was anesthetized with 30 mg/kg sodium pentobarbital, and a left flank incision was made to expose the kidney. The renal artery, renal vein, and the ureter were isolated and a gated sine wave electromagnetic flow transducer was placed on the renal artery adjacent to the aorta. A Biotronics flowmeter was utilized with the output recorded on a Grass recorder. A variable occluder was placed on the renal artery just distal to the flow probe, and a 20-gauge Teflon B-D angiocath was inserted into the renal artery distal to the occluder to measure renal arterial pressure. Care was taken in placing the angiocath into the renal artery to assure that renal blood flow was not compromised. For measurement of renal venous pressure, a catheter was inserted into the renal vein via the spermatic or ovarian vein and the catheter connected to a Statham pressure transducer. A variable occluder was placed around the renal vein just distal to the catheter to raise the venous pressure. The ureter was cannulated and the cannula connected to a drop sensor to monitor urine output and to a pressure transducer to measure ureteral pressure. The femoral vein was cannulated to allow infusion of an isotonic saline solution to match urine output, infusion of inulin, and infusion of 1.0 M mannitol. A tracheal cannula was inserted to facilitate respiration, and the carotid arteries were isolated.

Following this preparation, one or more of the following procedures were performed: 1) the renal artery was constricted to alter renal arterial pressure; 2) the renal vein was constricted to increase venous pressure; 3) the drop sensor was elevated to increase ureteral pressure; 4) 100–200 ml of a 1-M solution of mannitol was infused. The time required for the capsule pressure to reach a new equilibrium in response to one of the above procedures varied according to the length of time the capsule had been implanted and the magnitude of the pressure change. However, steady-state values were usually obtained within 3–5 min following achievement of steady state hemodynamic conditions and only steady-state values were recorded.

![Fig. 1. Response of implanted capsule pressure to a 1-ml infusion followed by a microliter withdrawal of fluid. Note that in both cases pressure returned slowly to base-line pressure.](http://ajplegacy.physiology.org/Downloadedfromhttp://ajplegacy.physiology.org/Downloadedfromhttp://ajplegacy.physiology.org/)
Several criteria of acceptability were imposed on the individual experiments. Typical autoregulatory behavior in response to changes in arterial pressure and to occlusion of the renal artery was required of the preparations (28). In addition, if the values for renal blood flow, glomerular filtration rate, and urine flow were found to be outside the normal range (31), the results were discarded. The average control values with the standard deviations for the acute experiments were as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood flow</td>
<td>3.82 ml/min per g kidney ± 0.94 (SD)</td>
</tr>
<tr>
<td>Glomerular filtration</td>
<td>0.69 ml/min per g kidney ± 0.33 (SD)</td>
</tr>
<tr>
<td>Urine flow</td>
<td>0.007 ml/min per g kidney ± 0.004 (SD)</td>
</tr>
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Upon termination of the experiment, the kidneys were excised, weighed, and examined. If the kidney was visibly inflamed or edematous or the capsule misplanted in any way, the results were discarded.

Analysis of inulin in the urine and plasma samples was performed by an automated anthrone method as previously reported (1). Calibration of the electromagnetic flowmeter transducer was performed at the end of each experiment by cannulating the renal artery and comparing timed blood collections to the recorder readings.

A Digital Equipment Corp. PDP-9 digital computer was used to facilitate data analysis and presentation of the results. The data were transposed to magnetic tape and stored. It could then be called as needed with the aid of FORTRAN programming, and the necessary calculations and statistical analyses were carried out.

RESULTS

Chronic measurement of renal interstitial fluid pressure using implanted capsule technique. A total of 156 measurements of implanted capsule pressures was made on 35 animals for as long as 80 days following surgery. Statistical analysis of the data demonstrated that there was no significant difference between the values obtained at different time periods following implantation. The overall average capsule pressure was calculated from these data by two different methods. In the first procedure a mean for each animal was calculated using the pressures recorded for that animal. These means were used to calculate an average and standard error of the mean. The second procedure used the individual pressures as independent data points, and an average and standard error of the mean were calculated. The two methods give almost identical results. The pressure calculated by the first method yielded an average renal interstitial fluid pressure of 6.2 ± 0.08 mm Hg (SEM). The second procedure gave an average renal interstitial fluid pressure of 6.0 ± 0.32 mm Hg (SEM).

Effect of arterial pressure changes on interstitial fluid pressure. The effect of changes in renal arterial pressure (RAP) on renal interstitial fluid pressure was studied by raising the venous pressure by closing the oculder placed around the renal vein. The vein was constricted; and when the venous pressure, the capsule pressure, and the urine output had reached new steady-state levels, the values were recorded. The average results of eight experiments are shown in Fig. 3.

Values were obtained over a venous pressure range of 5-40 mm Hg and grouped in 10-mm Hg venous pressure intervals. Over this venous pressure range, renal blood flow remained relatively constant in accordance with previous observations (25, 38, 40). Changes in venous pressure affected renal interstitial fluid pressure to a greater extent than changes in arterial pressure. Regression analysis demonstrated a highly significant relationship between

FIG. 3. Relationship between renal interstitial fluid pressure and renal arterial pressure. Table gives interval, average, standard deviation, and standard error of mean along with number of measurements in each pressure interval (SEM is demarcated on graph).
renal interstitial fluid pressure, and renal venous pressure ($P < .001$) yielding a regression equation of $\text{RIFP} = .34 \text{RVP} + 4.23$.

Effect of ureteral pressure changes on interstitial fluid pressure. The ureteral pressure (UP) was altered and maintained at an elevated pressure by connecting the ureteral catheter to a drop sensor and raising the drop sensor above the animal to establish the desired hydrostatic pressure. When the ureteral pressure, urine output, renal blood flow, and capsule pressure had reached steady states, the results were recorded. Figure 4 shows the average results of nine experiments in which ureteral pressure was varied over a range from 0 to 45 mm Hg. The data points were grouped in ureteral pressure intervals of 15 mm Hg to yield the average values. In agreement with previous observations, renal blood flow generally increased as the ureteral pressure increased (27, 28). The results of these experiments indicate the marked influence of changes in ureteral pressure on renal interstitial fluid pressure. Regression analysis of these results again demonstrated a highly significant relationship between renal interstitial fluid pressure and ureteral pressure ($P < .001$) with a resultant regression equation of $\text{RIFP} = .34 \text{UP} + 5.83$. Although it can be seen that changes in ureteral pressure and venous pressure are over 10 times as effective as arterial pressure changes in bringing about changes in renal interstitial fluid pressure, it should be noted that the changes in renal interstitial fluid pressure are not equal to the changes in either ureteral or venous pressure.

Effect of mannitol infusion on interstitial fluid pressure. Five animals were given an infusion of 100–200 ml of 1.0 M mannitol solution at a rate of 2–10 ml/min. Figure 5 shows a typical response of renal interstitial fluid pressure and urine flow increased in every experiment. In this series of experiments, the average renal interstitial fluid pressure increased from a control value of 8.5 to 19 mm Hg at the peak diuretic response. This load of mannitol caused a 15-fold increase in urine flow and an increase in renal blood flow of 45% in accord with previous observations (29).

**DISCUSSION**

A variety of techniques have been used by several investigators in an attempt to determine the functional significance of the renal interstitial compartment (9, 10, 20, 21, 31, 35, 36). The results obtained have varied considerably, presumably because of the techniques utilized, the experimental preparations, and the nature of the pressure actually measured.

It has been suggested that both the needle pressure method and the small pipette (100 ,u) technique can yield values indicative of the renal interstitial fluid pressure (9, 10, 20, 36). These values have ranged from 9 to 25 mm Hg with a mean value of about 14 mm Hg. However, it is unlikely that either method can be employed without resulting in at least some degree of tissue distortion. Indeed, to obtain a satisfactory measurement using these techniques, a minute quantity of fluid often must be injected into the tissues before a stable pressure can be achieved. According to the theoretical relationships among interstitial fluid pressure, solid tissue pressure, and total tissue pressure, when the solid elements of the tissue are separated as a result of fluid injection, the solid tissue pressure falls to zero, and the fluid pressure then measured has risen to equal total tissue pressure (17) rather than normal

**FIG. 3.** Relationship between renal interstitial fluid pressure and renal venous pressure. Table gives interval, average, standard deviation, and standard error of mean along with number of measurements in each pressure interval ($\text{SEM} \text{is demarcated on graph}$).

**FIG. 4.** Relationship between renal interstitial fluid pressure and ureteral pressure. Table gives interval, average, standard deviation, and standard error of mean along with number of measurements in each ureteral pressure interval ($\text{SEM} \text{is demarcated on graph}$).

**FIG. 5.** Typical response of renal interstitial fluid pressure and urine output to a 1 M mannitol infusion. Time is shown on bottom axis. Lines on RIFP response curve were electronically superimposed to mark spot at which urine output was measured.
interstitial fluid pressure. Also, because of the highly vascular nature of the kidney, damage to the capillaries and tubules is extremely difficult to avoid (36), and this can give erroneous values.

It has been suggested, too, that the intrarenal venous pressure can be used as an estimate of the renal tissue pressure (9, 11, 20). Pressures measured in this way agree well with those measured by the needle and especially well with those measured by the small pipette (10, 12). However, the intravascular pressure must theoretically be at least as great as the total tissue pressure (the algebraic sum of interstitial fluid pressure and solid tissue pressure). Otherwise the vessel would become totally occluded because of the well-known Starling resistor effect.

Finally, renal tissue pressure has been estimated by raising either the ureteral or venous pressure until renal blood flow begins to decrease (20, 21). The venous or ureteral pressure at which this occurs is then used as an estimate of the renal interstitial fluid pressure. Since it has been demonstrated by our data and that of others (29, 38, 40) that with increases in venous pressure up to as high as 50 mm Hg the renal blood flow (because of autoregulation) is virtually unchanged and that increases in ureteral pressure often increase renal blood flow (27, 28), it is almost certain that this method is unsatisfactory in normally responsive autoregulating preparations.

Recently Stromberg and Wiederhielm (34) have suggested that the implanted capsule does not measure the interstitial fluid pressure but rather measures an oncotic pressure difference across a tissue-lined membrane which is impermeable to tissue proteins. However, the restricted diffusion coefficient of albumin through this membrane has been measured and found to be 2.0 $\times$ 10^{-7} cm^2/sec (13) which represents very little restriction. This indicates that albumin can diffuse through the membrane at a rate about one-third that through pure water.

These same studies also give a reflection coefficient of 0.25 (13), which indicates that any acute change in albumin concentration yields an effect which is only one-fourth that possible for a totally impermeable membrane. It also indicates that the effect would be a transient one because of redistribution of albumin across the membrane.

In addition, Gibson and Gaar (8) have shown that the concentration of labeled albumin comes to equilibrium in the lymph, blood, and capsular fluid after a period of time. Gibson and Gaar also measured albumin to globulin ratios in lymph and capsular fluid and found them to be nearly identical (8). These results along with the results of Granger et al. (13) illustrate that if a membrane exists inside the capsule, it is indeed permeable to both fluids and albumin. With a membrane having a high permeability to protein, such as the capsular membrane, it is impossible to have a steady-state oncotic pressure gradient without a tremendous rate of continued fluid flow through the membrane. This is unreasonable because of the sequestered nature of the capsule cavity.

Since neither the above data nor the data of Stromberg and Wiederhielm were obtained from capsules implanted in the kidney, a test was run to determine the validity of measurements from capsules which had been implanted in the kidney. At the end of this series of experiments, there was an animal with two functioning capsules which had been implanted for 3.5 weeks. The pressure measured from these capsules was 2.5 and 3.5 mm Hg. The capsule in which the pressure measured 2.5 mm Hg was removed from the kidney leaving approximately 2 mm of tissue surrounding the capsule and catheter. It was placed in the bottom of a graduated cylinder and covered with isotonic saline. The capsule pressure was measured in the normal manner. A reference transducer was used to monitor the hydrostatic pressure in the graduated cylinder. Isotonic saline could be added or removed from the graduated cylinder to change the hydrostatic pressure and the response of the capsule noted. The pressure changes measured from the capsule were within the limits of transducer error at these small pressure levels (±10%). At the average pressure of 6 mm Hg obtained in this study, this means the pressure measured from the capsule should agree within 0.6 mm Hg with the hydrostatic pressure exerted by the interstitial fluid.

The most critical part of this test was the addition of 5 ml of concentrated albumin to the saline (Travenol—normal salt-poor human serum). The addition of the 5 ml concentrated albumin solution had a twofold effect on the fluid in the graduated cylinder. First, it increased the hydrostatic pressure by raising the level of fluid in the cylinder. Second, it increased the oncotic pressure of the fluid in the cylinder by 20 mm Hg. The capsule pressure could then behave in two ways. If the capsule were measuring hydrostatic pressure, the capsule pressure would increase to match the increase in hydrostatic pressure. If the capsule should behave as if it had an impermeable membrane, the pressure within the capsule would decrease due to the removal of fluid from the capsule by the osmotic effects of the albumin outside the capsule. Within 3 min the pressure measured from the capsule had risen to match the increase in hydrostatic pressure caused by the addition of fluid to the graduated cylinder. The capsule was opened and found to have a 3 x 7 mm cavity in the center which was filled with fluid. This experiment was repeated using a capsule from another animal which had been implanted for 2.5 weeks and gave identical results. The results indicate that the capsule is very capable of measuring changes in hydrostatic pressure and is not responsive to changes in the oncotic pressure of the fluid surrounding the capsule.

Use of the implanted capsule technique to estimate renal interstitial fluid pressure in the kidney is, however, not without several possible errors. Because of the small size of the capsule, its internal cavity fills with connective tissue more rapidly than occurs in standard capsules used in other tissues (15). In previous studies, it has been demonstrated that a minimum of 4 weeks is required before steady-state pressures can be obtained from the standard capsule (15, 26). Measurements taken before that time have usually read higher than the final steady-state measurements (15, 26). In this study the number of capsules that were responsive beyond the 4-week period was fewer than is usually the case.

Another problem involved in the use of these small capsules has been that some capsules became filled with a gel-like substance even while the capsule still seemed to be responsive. Previous studies have demonstrated that when
since this is the pressure responsible for fluid movement in the interstitium. This concept is supported by the results of the changes in renal "tissue" pressure. Although no effects on renal interstitial fluid pressure caused by alterations in renal arterial pressure. Several investigators have suggested that changes in the renal arterial pressure in some way affect the net rate of fluid and sodium reabsorption from the tubules (2-4, 22, 32). Specifically, Bank and colleagues (2, 3, 22) have given detailed consideration to the possibility that diuretic responses observed consequent to increased arterial pressure are perhaps largely related to the changes in renal "tissue" pressure. Although no distinction among the types of tissue pressure was made, it is assumed that renal interstitial fluid pressure was inferred since this is the pressure responsible for fluid movement in the interstitium. This concept is supported by the results of studies reported in this study may overestimate the true renal interstitial fluid pressure. However, regardless of the cause of the increased pressure, these results fit with the suggestions of several previous investigators that renal interstitial fluid pressure changes affect the net diuretic response to infusion of electrolyte solutions (4, 5, 23). Also, one might postulate that changes in the renal interstitial fluid pressure contribute to the massive diuresis resulting from mannitol solution infusions.

The results of these experiments thus indicate that the implanted capsule method, although not without drawbacks, is perhaps the most satisfactory method now available for estimating renal interstitial fluid pressure. Also, it has been demonstrated that the capsule pressure measurements are dynamic and respond to changes in arterial, venous, and ureteral pressures and to infusions of mannitol. These findings are consonant with the hypothesis that changes in renal interstitial fluid pressure may have an important role in affecting net fluid movement through its contribution to the overall balance of forces across the tubular and peritubular capillary walls.

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