Changes in composition of the urine in ureter and bladder at low urine flow

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LEVINSKY, NORMAN G. AND ROBERT W. BERLINER. Changes in composition of the urine in ureter and bladder at low urine flow. Am. J. Physiol. 196(3): 549-553. 1959.—The movements of water and solutes across the ureter and bladder have been studied under conditions approximating those routinely used in physiological experiments at low urine flows. When the ureter and bladder are perfused at flows of less than 1 ml/min. movements of water, urea, sodium, potassium, chloride, creatinine and hydrogen ion occur. The magnitude of these changes increases as the rate of perfusion is decreased or when urine is allowed to pool in the bladder. All movements of water and solute are in the direction of their concentration gradients. The movements are not affected by changes in antidiuretic activity, anesthesia or surgical manipulation. Fluid collected from an indwelling Foley catheter draining continuously at a rate of 0.1 ml/min. may have an osmolality approximately 10\% lower than that of the fluid entering the ureter and a urea concentration about 15\% lower. When urine is allowed to accumulate in the bladder during 30-minute periods at the same flows, the changes may be 50-100\% greater. At low urine flows, the composition of urine collected from the bladder does not accurately represent the composition of the urine as it leaves the kidney.

IT IS USUALLY IMPLICITLY ASSUMED in the study of renal function that the composition of urine does not change as it passes through the ureters and the bladder. Yet an extensive literature indicates that, under some circumstances at least, the lower urinary tract is by no means a perfect barrier to the movement of water and solutes. Data presented in this paper emphasize that normal constituents of the urine may pass across the ureters and bladder under physiologic conditions. Consideration of these movements is of practical significance in the interpretation of results obtained in studies of kidney function at low urine flows.

METHODS

A variety of experimental preparations have been used to duplicate insofar as possible the usual conditions in studies of kidney function. To eliminate artefacts due to surgical manipulation and anesthesia, a number of dogs were prepared several days prior to experiments in one of the following ways. a) For perfusion of a ureter and the bladder, one kidney was removed and a polyethylene catheter (o.d. 1.22 or 1.52 mm) sewn in place in the free end of ureter. Then, either a bladder-splitting operation (1) was performed so that the perfusate could be collected from a nylon funnel in the homolateral half-bladder; or a reversibly inflatable clamp was placed around the other ureter so that urine flow could be shut off during collection of the perfusate from a catheter in the bladder. b) To permit perfusion of the ureter alone, a nephrectomy was done and a polyethylene catheter was positioned in the free end of the ureter. Another catheter was introduced about 1 cm into the distal end of the ureter through the ureteral orifice and was led to the outside through the urethra. Each catheter was held in place by two or three stitches taken diametrically through the ureter and catheter and loosely tied. To avoid ischemia, no constricting circumferential ties were used. At autopsy, the operated ureter appeared to be in good condition.

Experiments were also done in dogs anesthetized with pentobarbital. In this case, one ureter was cut and tied close to the bladder; the other ureter was cut near the kidney and cannulated about 1 cm in the direction of the bladder with polyethylene tubing. The perfusate was collected via a urethral catheter in the bladder. Urine from both kidneys was drained to the outside by means of catheters in the proximal stumps of the ureters.

Female mongrel dogs, each weighing 10-15 kg, were used. Except as otherwise noted, all dogs had been dehydrated overnight and had been given 3 \( \mu \) of Pitressin tannate in oil about 16 hours prior to an experiment. Unanesthetized dogs were standing during experiments, partially supported by slings. Anesthetized dogs were either supported in the standing position by slings or were lying supine. In each experiment, fluid was perfused through the lower urinary tract at several rates by means of a constant infusion pump. The perfusion fluid was in most cases an 'artificial urine', containing urea, sodium and potassium chloride, inulin and sometimes creatinine. The pH of this fluid was adjusted to between 4 and 5 with acetic acid in some experiments. In a few experiments, the dog's own urine, to which inulin had

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been added, was used as the perfusion fluid. In some studies an intravenous infusion of creatinine in 0.9% saline was given at a constant rate estimated to result in a blood creatinine level of 15 mg%. Immediately before each collection period, the bladder was washed several times with the original perfusion fluid. Except as otherwise noted, the catheter in the bladder was allowed to drain freely into a graduate during collection periods. Collections from the bladder were begun and ended by air washouts. Therefore, collections were probably contaminated to some extent with the original perfusion fluid and the changes in concentration reported are minimum values. The concentrations of urea, sodium, potassium, inulin and sometimes of chloride and creatinine were measured. The methods used for these analyses have been listed elsewhere (1, (ms. in preparation by Levinsky, Davidson and Berliner)). In a few cases, pH was measured at room temperature and after exposure to room air by means of a Cambridge model R pH meter. Change in inulin concentration was used as a measure of change in volume. In preliminary experiments, 97 and 99% of a measured amount of inulin placed in the bladder for 30 minutes was recovered.

RESULTS

The experiment summarized in table 1 was performed on an anesthetized dog lying supine. The dog’s own urine was perfused through a ureter and the bladder and was collected via a straight shellac urethral catheter. Each collection period was 30 minutes long. As would be expected, the greatest changes in urine composition occurred at the lowest flows. Urea concentration fell some 20%, and the osmolality decreased about 15%. Sodium and chloride concentrations increased some 15%, while the concentration of potassium decreased to a similar extent. Part of the concentration changes was due to an increase in volume; however, there was a net change in the concentration of each solute, when a correction was made for volume change.

The results of experiments in acutely prepared, anesthetized dogs and in both kinds of unanesthetized chronic preparations were qualitatively similar. The average changes in volume and solute concentration in all the experiments done with one type of perfusion fluid are shown in figure 1. In these studies the ureter and bladder were perfused with an ‘artificial urine,’ of the composition shown in the legend to figure 1. As flow was decreased stepwise below 1.1 ml/min., the changes in volume and solute concentration and the net solute movement became progressively greater. The data in figure 2 presenting the average of two studies in a single unanesthetized dog show that similar changes occurred when only the ureter was perfused by an artificial urine. The results of experiments in which the ureter and bladder or the ureter alone were perfused with a fluid containing 200 μM/ml urea and unchanged amounts of the other solutes were similar to the above experiments as to the relative changes in urea concentration. When flow is less than 1.1 ml/min., net loss of creatinine may also occur. In the experiments shown in figure 3, a blood level of about 15 mg% of creatinine was maintained. Net losses of creatinine were found over a wide range of urine/plasma (U/P) creatinine ratios, encompassing those usually found in physiological experiments. At a given flow there was no relation between the U/P creatinine and the absolute or percentage loss of creatinine. However, the experiments at different U/P ratios were done in different dogs, so that biological variability between dogs may to some extent have obscured such a relationship.

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<th>Table 1. Perfusion of Urea Through Ureter and Bladder</th>
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<td>Perfusion Rate</td>
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FIG. 1. Perfusion of ureter and bladder. Approximate composition of perfusion fluid was urea, 1000 μM/ml; NaCl, 50 μM/ml; KCl, 200 μM/ml; inulin, 100 mg%. Data are from 4 experiments in 4 different dogs (2 anesthetized, 1 of each unanesthetized preparation described in Methods). Numbers in parentheses are number of collection periods at each perfusion rate averaged to give points shown. All points represent percentage change from composition of original perfusate. Closed circles show observed changes, open circles the net changes after correction for water movement.
COMPOSITION OF URINE AT LOW URINE FLOW

Three experiments in which pH changes in an acid artificial urine were measured are plotted in figure 4. In two experiments, in two different anesthetized dogs, both the ureter and bladder were perfused. In the other experiment, only the ureter was perfused in an unanesthetized chronic preparation. The change in pH depended both on the rate of flow and on the concentration of buffer (creatinine) present. At any given concentration of buffer, the pH change increased with decreasing flow. Using the value 4.97 as the pKa of creatinine in the Henderson-Hasselbalch equation, net loss of hydrogen can be calculated as between 5 and 8 μmol at the four lowest flows in the experiment plotted with open circles in figure 4. At the corresponding flows in the experiment plotted with closed circles, the loss of hydrogen was between 1.5 and 4.5 μmol. Equilibration of these perfusion fluids with 5% CO2 lowered pH by less than 0.05 U.

The longer the time during which the urine is exposed to the bladder, the greater the changes in urine composition which occur. In figure 5 a comparison is shown of two methods commonly used to collect urine during physiological experiments. The dogs in these studies were all in the standing position, and urine was collected via a Foley catheter in the bladder. A 30-minute collection was first made with the catheter open and draining freely (open circles); then the catheter was clamped shut and the perfusion fluid was allowed to pool in the bladder during another 30-minute collection period (closed circles). When the catheter was open, about one half to three fourths of the final total collection drained spontaneously into the collection vessel during the 30-minute period. At each speed, the changes in fluid composition were more marked when the catheter was closed and the fluid retained in the bladder during the collection period.

An experiment showing that antidiuretic activity does not alter the movements of water and solutes across the ureter and bladder is illustrated in the upper part of figure 6. This experiment was done in an unanesthetized dog prepared previously by the bladder-splitting procedure. Two 30-minute collection periods of fluid perfused at 0.06 ml/min. were obtained during maximum water diuresis, as shown by the osmolality of the urine from the other half-bladder (70 mOs/kg H2O). 50 μg/kg/hr. of vasopressin (Pitressin) were then given in an intravenous infusion, and after 30 minutes two more perfusion fluid collections were made. During these periods, the osmolality of the dog’s urine was 650. No significant difference between the movements of water and solutes was found when the collections in the presence and absence of antidiuretic activity were compared.

In the lower part of figure 6, an experiment performed on the same dog to evaluate the effects of anesthesia is plotted. Perfusion fluid was collected at 0.06 ml/min.
FIG. 5. Effect of retention of urine in bladder on changes in composition. A single experiment at each perfusion rate is represented. Consecutive collections at the same perfusion rate were made with the Foley catheter open and draining freely (○) and closed, allowing urine to pool in the bladder (●). The points represent percentage changes from the composition of the original perfusate (urea, 1000 μg/ml; NaCl, 50 μg/ml; KCl, 200 μg/ml; inulin, 100 mg%; creatinine, 100 μg/ml).

before and after the dog was anesthetized with pentobarbital given intravenously. A deep stage of anesthesia was produced in which the corneal reflexes were absent. No difference in water and solute movement across the ureter and bladder was noted between the conscious and the deeply anesthetized states.

DISCUSSION

In the interpretation of studies of kidney function, no significance is usually attached to the fact that the urine must pass through the ureters and bladder before it can be collected for analysis. The present studies suggest that at flows of 1 ml/min. or more it is safe to consider the lower urinary tract as essentially a conduit for urine. At lower flows, however, and particularly at flows of less than 0.25 ml/min., marked changes in urine composition occur during transit through the bladder and ureters. Movements of water, urea, sodium, potassium, chloride, creatinine and hydrogen ion in the direction of their concentration gradients have been found. One cannot equate the urine collected from a catheter in the bladder with the urine passed from the kidney, when precise analysis is desired.

An extensive literature, summarized by Englund (2), attests that the ureters and bladder arc by no means perfect barriers to the movement of water and solutes. However, one or another objection can be raised as to the practical physiological significance of most of these studies. In many, the test fluids were exposed to the bladder for prolonged periods of up to several hours. For example, such was the case in the studies of Vickers and Marshall (3) in the rabbit, and of Maluf (4) in man. In some, unphysiologic or possibly toxic test materials or normal urine constituents in concentrations outside the physiologic range were introduced into the bladder (e.g. (5, 6)). Most of the studies were performed on anesthetized animals immediately after surgical manipulation of the urinary tract. In Garby and Ulfendahl’s studies (7), for example, anesthetized rabbits were used in which the perfused ureter had been tied at both ends, possibly restricting blood supply. In several recent studies employing radioisotopes, it is not clear whether the changes in isotopic concentration reported represent merely exchange of radioactive for stable isotope or whether a net change in total concentration occurred (e.g. (8)). The present studies were designed to determine the changes in the composition of normal hypertonic urine as it passes through the lower urinary tract under the conditions usually found in physiological experiments. Marked changes in urine composition were found to occur even when unanesthetized, previously operated dogs were studied. These results emphasize the necessity for caution in the interpretation of experiments done at low urine flows, or those in which urine is allowed to pool in the bladder during collection periods.

Because urea moves very rapidly out of the ureter and bladder from the high concentrations normally found in hypertonic urine, particular caution must be exercised in interpreting data on urea excretion at low flows. For example, in the studies of Shannon (9) relating urea excretion to urine flow, urine was allowed to collect in the bladder throughout clearance periods of 30 minutes or more at low urine flows. Considerable loss of urea and of creatinine (used as a measure of water reabsorption) would be expected under these conditions. Again, Ullrich (10) has reported that in dehydrated dogs the urinary urea concentration is about the same as the concentration in the tissue water of the renal papilla. However, in these studies the urine was collected for analysis after it had been allowed to pool in the bladder for some time before and a few minutes

FIG. 6. Effects of vasopressin (upper half of fig.) and anesthesia (lower half of fig.) on changes in urine composition during perfusion of ureter and bladder. The points represent percentage changes from the composition of the original perfusate (same as that in fig. 1).
after death. From the data presented herein, the urea concentration in urine leaving the papilla would be expected to be 10–40% higher than the concentration in urine collected in this way.

It should be noted that, although accumulation of urine in the bladder at low flows during periods of the length usually used in acute renal function studies yields greater changes in urine concentration than free drainage of the urine, continued accumulation would be expected to produce diminishing changes in composition as the total volume in the bladder increases and the surface-volume ratio is lowered. Were it not for this, it would presumably be impossible to obtain the frequently very high concentration observed in dog urine accumulated overnight in the bladder.

REFERENCES

6. COHNHEIM, O. Z. Physiol. 41: 331, 1901.

The present results also indicate that creatinine is not an exact measure of the glomerular filtration rate at low flows. The studies of Ladd and associates (11) showed that when urine flow is abruptly reduced by acutely lowering the filtration rate, the ratio of the clearances of creatinine to inulin, normally 0.94, may fall as low as 0.20. In unpublished studies, we have also found that the creatinine/inulin clearance ratio falls under similar circumstances, although the minimum value in our experiments was 0.80. While passive reabsorption of creatinine in the renal tubule, as suggested by Ladd et al., probably accounts in part for these results, loss of creatinine from the lower urinary tract may also play a role.