THE PATHOGENESIS OF PROTEINURIA IN THE ACUTELY CONGESTED KIDNEY[1]

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The appearance of proteinuria in patients suffering from congestive heart failure is a common clinical occurrence. Since such patients, without any intrinsic renal disease, frequently have both an elevated renal venous pressure and a reduced renal blood flow (1), it would seem that either one or both of these factors may lead to proteinuria.

Proteinuria has been produced experimentally by partial obstruction either of the renal artery or of the renal vein (2–5). In most of this work, however, studies of renal hemodynamics were incomplete, or when adequate pressure and blood flow measurements were made (6, 7), the experiments were such that it was impossible to determine specifically which hemodynamic factor was responsible for the appearance of the proteinuria.

The present study was undertaken in an attempt to define further the hemodynamic changes responsible for the excretion of protein by the acutely congested kidney.

METHODS

Experiments were performed on 26 adult female mongrel dogs weighing between 10 kg. and 30 kg. The animals were anesthetized by the intravenous administration of 0.45 to 0.79 ml. per kilogram of a 6 per cent solution of sodium pentobarbital. The abdomen was opened through a midline incision. A plastic catheter was tied in each ureter and an adjustable screw clamp was placed around the left renal vein. A catheter was passed *via* the right jugular vein into the left renal vein and placed so that its tip lay distal to the clamp. This catheter was connected to a water manometer allowing continuous measurement of the pressure in the left renal vein. A detailed description of the clamp and the technique used has been published previously (8). A continuous recording of the mean arterial blood pressure was made by a mercury manometer connected to the proximal end of the left femoral artery.

The estimations of renal plasma flow (RPF) and glomerular filtration rate (GFR) for each kidney were made by determining the clearances of para-aminohippurate (PAH) and exogenous creatinine, respectively. Blood samples were drawn at the midpoint of each clearance period from the right femoral artery through an indwelling needle.

During the operative procedure the animal was given intravenously a priming dose of 1.5 grams of creatinine dissolved in 30 ml. of water. This was followed by a sustaining infusion of an 0.85 per cent NaCl solution delivered at a constant rate of 3 or 5 ml. per minute by a Bowman Pump for the remainder of the experiment. This sustaining infusion contained sufficient amounts of creatinine and PAH so that these substances were delivered at rates of 20 mg. of creatinine per minute and 3 mg. of PAH per minute. In some instances an additional infusion of NaCl solution (0.85 or 1.5 per cent) was given during the course of the experiment. The reason for this will be discussed later.

After completion of the operative procedure the animal was allowed to recover for about 30 minutes. One or more control urine samples were then collected in order to measure the clearances and determine the presence of proteinuria. The clamp was then tightened until the pressure in the left renal vein rose to the desired level. After the pressure had been elevated for 15 to 30 minutes, consecutive urine samples were collected until proteinuria appeared or until the pressure had been elevated for 1 to approximately 3 hours without the occurrence of proteinuria. The clamp was then released allowing the pressure in the left renal vein to fall freely. After an interval of time at least sufficient to allow the renal dead space to be cleared, one or more recovery samples were collected.

Creatinine concentration in urine and plasma was determined by the method of Kennedy, Hilton, and Berliner (9). PAH concentration in urine and plasma was determined by the method of Smith, Finkelstein, Aliminosa, Crawford, and Graber (10).

The method used to determine the concentration of protein in urine was a modification of the method of

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Looney and Walsh (11). To 2 ml. of acidified urine were added 8 ml. of a 3 per cent sulfosalicylic acid solution. Protein was considered to be present only if a turbidity visible to the naked eye developed after the addition of the sulfosalicylic acid. The turbid solution was read against a water blank in a Coleman Junior spectrophotometer set at a wave length of 400 λ and compared with known protein standards containing from 10 to 100 mg. of protein per cent. The standard solutions obey Beer's Law at this wave length. Because urinary chromogens also absorb light at this wave length, the urine from the right (control) kidney was used as the blank and its light absorption was subtracted from that of the left in order to determine the protein concentration. The effect of differences in the chromogen concentration between the urine from the left and right kidneys was corrected by diluting the urine from the kidney with the lesser urine flow to equal in volume the urine from the opposite kidney. It was observed that after such a dilution the light absorption due to chromogens in the urine from the left and right kidneys agreed within 10 per cent. Since the urine from the right kidney never developed turbidity, its light absorption was considered to be due entirely to non-protein material. Furthermore, a series of experiments was performed utilizing this procedure to analyze urine to which known amounts of pooled dog plasma protein had been added. Recovery within 5 per cent was obtained at concentrations ranging from 10 to 100 mg. per cent.

The urine samples were not examined microscopically. When the urine appeared cloudy it was centrifuged. Occasionally red blood cells appeared in the centrifugate of the urine from one or both kidneys. In these instances if the supernatant fluid did not contain protein, the period was included in the negative results. If there was protein in the supernatant fluid the period was discarded since under the experimental conditions one could never be certain whether the hematuria had its origin in the kidneys or whether it was the result of trauma to the ureters by the catheter tips.

RESULTS

Thirty-two experiments were performed in twenty-six animals. Figure 1 shows the data obtained. The average control pressure in the left renal vein was 115 mm. of water and, as can be seen in Figure 1, the control venous pressure ranged between 65 and 175 mm. of water. After the pressure had been raised in the left renal vein, proteinuria appeared on the left side in 21 of the 32 experiments. Protein did not appear in the

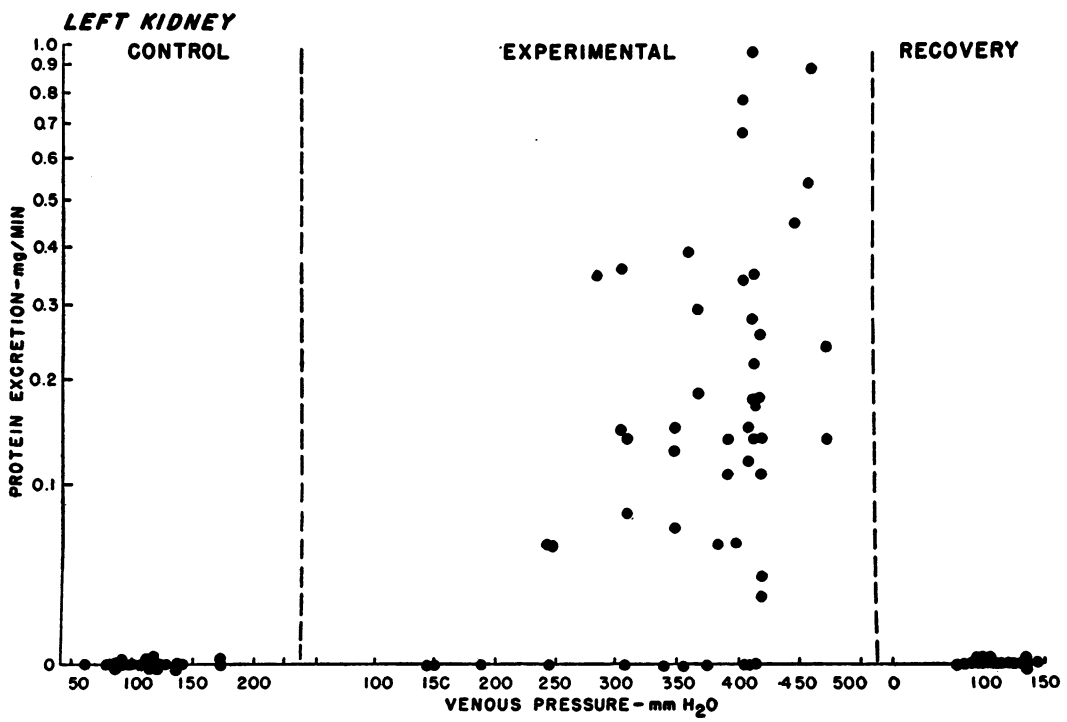

FIG. 1. EFFECT OF THE LEVEL OF LEFT RENAL VENOUS PRESSURE ON THE RATE OF PROTEIN EXCRETION BY THE LEFT KIDNEY

Along the abscissa is plotted the venous pressure in mm. of water and along the ordinate is plotted protein excretion expressed in mg. per minute. Each dot represents one collection period.

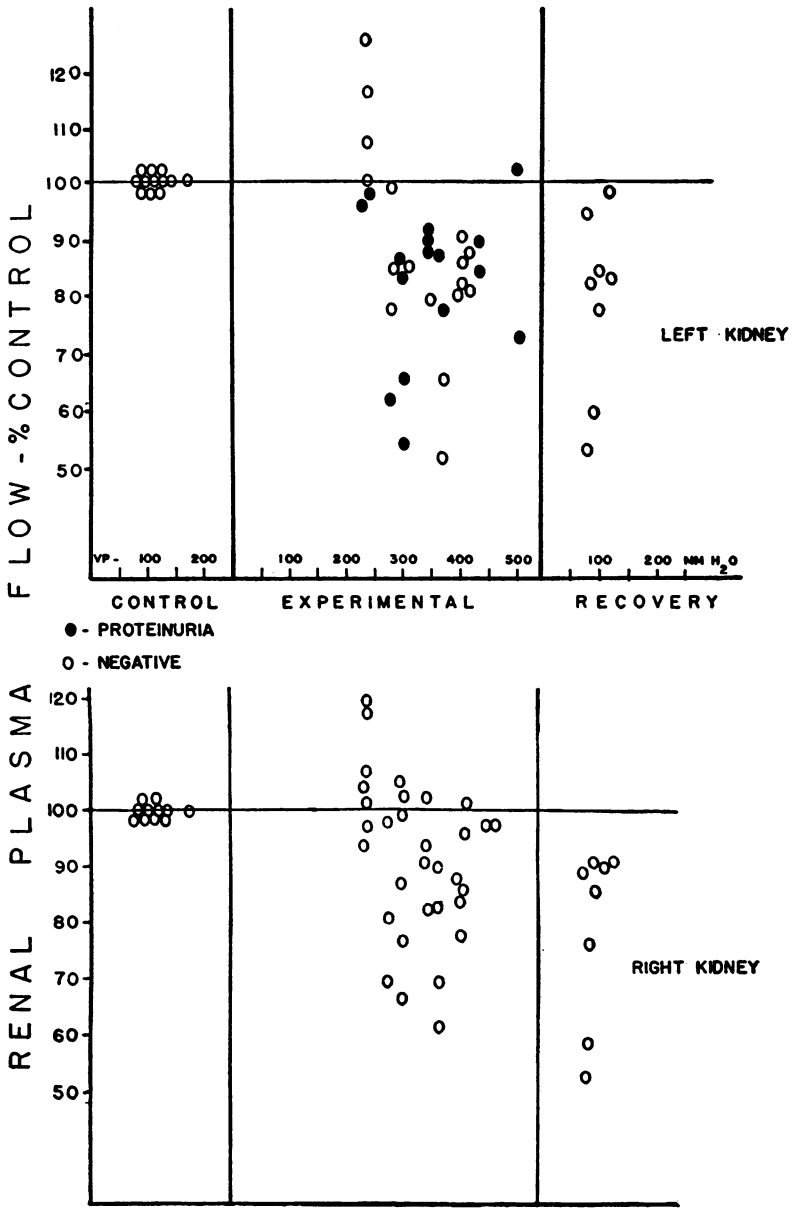

FIG. 2. SIMULTANEOUS CHANGES OF RPF IN THE LEFT KIDNEY (UPPER PART OF FIGURE) AND IN THE RIGHT KIDNEY (LOWER PART OF FIGURE) DURING EXPERIMENTS IN WHICH THE PRESSURE WAS RAISED IN THE LEFT RENAL VEIN ONLY

Along the abscissa of the upper part of the figure are plotted the levels of the left renal venous pressure expressed in mm. of water during the control, experimental, and recovery periods. Along the ordinate of the upper and lower parts of the figure are plotted the values for the RPF in the left and in the right kidneys expressed as the percentage of the control value in each kidney. Each open circle represents a clearance period during which no proteinuria occurred. Each closed circle represents a clearance period during which proteinuria occurred.

urine when the pressure in the left renal vein was less than 245 mm. of water. At pressures between 245 and 420 mm. of water, the left kidney excreted protein in 17 of 27 experiments. At pressures above 420 mm. of water, proteinuria always appeared. Protein appeared in the urine within one hour after the venous pressure was raised in 18 of the 21 positive experiments. In the remaining three experiments the proteinuria appeared between 61 and 75 minutes, 80 and 110 minutes, and 224 and 234 minutes, respectively. In the 11 experiments in which no proteinuria developed, the urine samples were collected after the venous pressure had been elevated for at least one hour. The time during which the venous pressure was kept elevated in these 11 negative experiments ranged between 66 and 215 minutes, the average being 113 minutes. Following release of the clamp, the left renal venous pressure fell immediately to within the range of control values, the average pressure during the recovery period being 110 mm. of water. The urine collection during recovery was begun within 9 to 30 minutes after release of the clamp in all but one experiment in which, by mistake, urine collection was not started until 57 minutes after the clamp had been released. Protein was never present in any of the recovery urine samples collected as stated above. At no time did the right or control kidney excrete protein in the urine.

Figure 2 shows the changes in RPF which occurred in the first 15 experiments, performed on 11 dogs. During these 15 experiments, 33 clearance periods were observed while the left renal venous pressure was elevated. Proteinuria occurred in 16 of these 33 periods. These 16 positive experimental clearance periods were obtained from 9 experiments on 8 dogs. As can be seen in

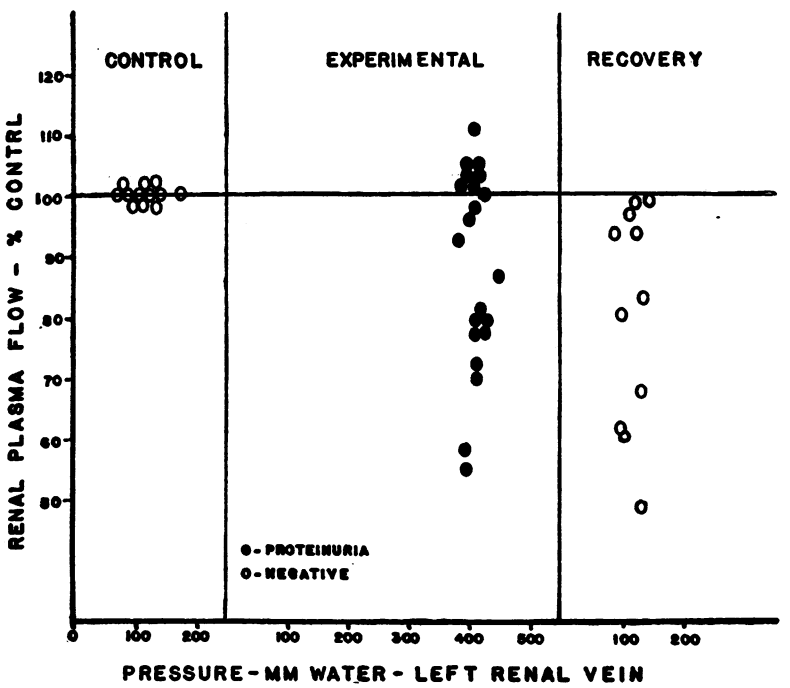

FIG. 3. CHANGES OF RPF IN THE LEFT KIDNEY DURING EXPERIMENTS IN WHICH THE PRESSURE WAS RAISED IN THE LEFT RENAL VEIN

Along the abscissa are plotted the levels of the left renal venous pressure expressed in mm. of water during the control, experimental, and recovery periods. Along the ordinate are plotted the values for the RPF in the left kidney expressed as the percentage of the control value. Each open circle represents a clearance period during which no proteinuria occurred. Each closed circle represents a clearance period during which proteinuria occurred. The simultaneous changes in the right RPF are not plotted in this figure.

Figure 2, the appearance of proteinuria was associated with significant falls in the RPF in 13 of these 16 periods. In the remaining 3 periods, from 2 experiments on the same animal, proteinuria developed without significant change in the RPF. In 5 of the 13 periods in which proteinuria was associated with a fall in the RPF, the RPF fell equally in both kidneys while in the remaining 8 periods the flow fell to a somewhat greater degree in the left kidney than in the right. Although the RPF remained below control level in both kidneys during the recovery periods, protein disappeared from the urine of the left kidney.

A second series of 11 experiments on 10 animals was performed in which attempts were made to prevent the fall in the RPF by shortening the experiments and by infusing additional NaCl solution during the course of the experiments. Table I shows the protocol of one of these experiments. In this second series of 11 experiments, 29 experimental clearance periods were observed and proteinuria was present in 21 of these 29 periods. The data from these 21 clearance periods are shown in Figure 3. In 11 periods on 5 animals, the RPF either did not change or rose slightly during the experimental periods. In the other 10 periods on 5 animals, the RPF fell below control values.

The arterial blood pressure was recorded in 24 experiments on 21 dogs. The pressure remained within 10 mm. of mercury of its control level in 16 of these 24 experiments. It rose in 3 experiments an average of 26 mm. of mercury and fell in 5 experiments an average of 23 mm. of mercury.

Incidentally, the present experiments confirm the previous observations (2, 6, 8) that elevation of the renal venous pressure decreases the flow of urine.

DISCUSSION

It is apparent that in acute experiments elevation of the renal venous pressure to 245 mm. of water or higher, frequently caused otherwise normal kidneys to excrete protein. The proteinuria, moreover, appeared less than one hour after elevation of the venous pressure in most experiments and cleared very rapidly after the venous constriction had been released. Nonetheless, in view of the 3 experiments in which the protein appeared only after longer periods of renal vein constriction, one cannot exclude the duration of the venous pressure elevation as a factor of importance. Analysis of the data obtained in those experiments in which proteinuria occurred, failed to reveal any quantitative relationship between the height of the venous pressure and the amount of protein excreted. However, it must be kept in mind that the duration of the venous pressure elevation was not kept constant in the different experiments and that the effect of different levels of venous pressure on the protein excretion was not studied in the same dog. For these reasons a quantitative correlation between venous pressure and proteinuria cannot be excluded.

As to the hemodynamic change or changes which led to the proteinuria, one possibility was that the venous congestion produced proteinuria by decreasing the renal blood flow. In experiments on a dog heart-lung-double-kidney preparation in which the venous pressure was raised in one kidney while in the contralateral kidney the perfusion pressure was reduced sufficiently to result in an equal urine flow from the two kidneys, Winton (6) observed three occasions on which the congested kidney excreted protein while the urine from the kidney subjected to a reduced perfusion pressure contained no protein. This suggests that the elevation of the venous pressure was the critical factor leading to proteinuria. In Winton's preparations, however, the blood flow was always less in the congested kidney than in the contralateral kidney, and since Starr (5) has reported proteinuria following compression of the renal artery alone, reduction in blood flow could not be excluded as a causative factor of the proteinuria in Winton's experiments.

In the present series of 15 experiments plotted in Figure 2, proteinuria was usually associated with significant falls in the RPF. However, it seemed unlikely that in these experiments the reduction in blood flow was the only cause of the proteinuria since protein was never excreted by the right kidney although the decrease of the RPF in the right kidney was comparable to that of the RPF in the left kidney. Furthermore, following release of the venous constriction, the proteinuria always disappeared promptly despite the fact that the RPF remained depressed or fell even further during the recovery periods.

Although a reduction in renal blood flow could

TABLE I

Protocol of one of the experiments plotted in Figure 3

Time (*minutes*)	Pressure in left renal vein (*mm. Hg*)	Protein excretion (*mg./min.*) L	R	Creatinine clearance (*ml./min.*) L	R	Renal plasma flow (*ml./min.*) L	R	Filtration fraction L	R	Mean arterial blood pressure (*mm. Hg*)	Left total renal resistance*
Weight:	16.0 kg.										
−41	Primer: Creatinine 1.5 grams										
−40	Start of administration of infusion No. 1 (0.85% NaCl solution containing 0.6% of creatinine and 0.1% of PAH) at rate of 3 ml./min.										
−37	Start of administration of infusion No. 2 (0.85% NaCl solution) at rate of 1 ml./min.										
0–15	9	0	0	30	29	78	78	.38	.37	164	1.99
16	31										
35–55	31	.22	0	29	29	78	78	.37	.37	158	1.63
55–65	31	.18	0	30	30	79	77	.38	.39	157	1.59
65	Increase rate of administration of infusion No. 2 to 5 ml./min.										
70–90	31	.28	0	29	28	81	75	.36	.37	156	1.54
90	Reduce rate of administration of infusion No. 2 to 1 ml./min.										
90–110	31	.35	0	27	27	76	74	.36	.37	156	1.65
117	10										
130–150	9	0	0	28	27	73	71	.38	.38	162	2.10

* Total renal resistance $R = \frac{\text{Mean Arterial Pressure (mm. Hg)} - \text{Renal Venous Pressure (mm. Hg)}}{\text{RPF (ml./min.)}}$.

not be the only factor leading to the excretion of protein in these experiments, it remained possible that the combination of an elevated venous pressure and a reduced blood flow was necessary for the appearance of proteinuria (7). However, as shown in Figure 2, proteinuria occurred in 3 periods during which the left renal venous pressure was raised and the RPF had not changed. This observation suggested that the elevation of the venous pressure alone might have been the only cause of proteinuria. That this latter view was correct was confirmed by the results of the series of experiments plotted in Figure 3 in which elevation of the renal venous pressure caused proteinuria even when the RPF remained the same or rose slightly.

In view of the fact that Adrenalin® and ephedrine can induce proteinuria, presumably by causing renal vasoconstriction (5), one wonders whether elevation of the venous pressure might not act by inducing such a vasoconstriction. This mechanism seemed unlikely. Indeed, in the series of experiments of Figure 2, protein was never excreted by the right kidney although in some of these experiments there was evidence of vasoconstriction in this kidney since the arterial blood pressure remained relatively constant while the RPF fell and the filtration fraction (FF) rose. As a matter of fact, decreases of RPF as marked as 50 per cent were not accompanied by proteinuria. Furthermore, in the 5 experiments of Figure 3 in which venous pressure elevation induced proteinuria in the presence of an unchanging or rising RPF, proteinuria occurred in the face of a decreasing total renal resistance in all 5 cases, since the arterial blood pressure remained constant while the RPF remained unchanged or rose and the FF decreased. In these 5 experiments one must postulate dilatation at least of the efferent arteriole.[5] Therefore, it appears that at least in these experiments, the proteinuria was due to the elevation of renal venous pressure *per se* and not to renal vasoconstriction or decreased renal blood flow induced by the elevation of the venous pressure.

SUMMARY

In an experimental study of the pathogenesis of proteinuria in the acutely congested kidney of the anesthetized dog, it was found that:

1. Proteinuria appeared frequently following acute elevation of the renal venous pressure to levels of 250 mm. of water or higher;

[5] No attempt was made to calculate separately the resistance of the different segments of the renal vascular bed because under the conditions prevailing it appeared doubtful that Gomez' equations (12) were applicable.

2. Proteinuria occurred within one hour following elevation of the renal venous pressure in most animals, and disappeared promptly upon lowering the venous pressure to control levels;

3. Proteinuria appeared to be due to the rise in venous pressure and independent of changes in renal blood flow.

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