EFFECT OF INCREASED RENAL VENOUS PRESSURE ON RENAL FUNCTION

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THE formation of edema in cardiac failure was assumed for many years to be secondary to an increase in venous pressure. According to this hypothesis the major factor causing water and salt retention was extrarenal; the increased hydrostatic pressure forced fluid out of the vascular compartment into the tissue spaces and thus made this fluid unavailable for excretion. The lesser, or renal factor, leading to the oliguria of cardiac failure was supposedly the result of renal congestion caused by the increased venous pressure (1). In 1933 Rowntree, Fitz and Geraghty (2) studied the effects of chronic passive congestion of the kidney on renal function in dogs. They applied a band about the left renal vein and collected urine from the two kidneys separately through ureteral catheters. They observed in some dogs little change in urine flow on the left but a 20 to 40 per cent reduction in phenolsulphonphthalein (PSP) excretion and a diminished urine chloride concentration and chloride output. When they performed a right nephrectomy and then banded the left renal vein, there was a reduction in salt output without change in PSP excretion and no consistent change in urine flow.

In 1937 Winton (3) reviewed the physical factors governing urine flow. On the basis of his experiments in animals, as well as the work of others, he concluded that

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compression of the renal vein with subsequent renal congestion leads to a reduction in urine flow and chloride excretion. The findings were believed to result from a partial obstruction to the flow of urine through the tubules by the increased intra-renal pressure. Studies have been conducted on the effects of increased intrabdominal pressure on renal function (4-7). Reduction in urine flow and sodium excretion (8) have been demonstrated but the results are difficult to evaluate since the pressure in the renal pelvis as well as the pressure in the renal vein were increased.

Since the introduction of renal-clearance techniques the mechanisms involved in the renal retention of sodium in cardiac failure have received considerable attention. Warren and Stead (9), Merrill (10), Mokotoff, Ross and Leiter (11) and Stead, Warren and Brannon (12), have suggested that in many patients reduced sodium excretion is related to a reduction in glomerular filtration rate, especially following muscular activity (13). Other workers believe that the decreased sodium excretion is not entirely related to filtration rate but is related to an increased rate of sodium reabsorption (14-17). In accordance with classical concepts elevated venous pressure has been suggested as a possible cause (14, 18). The present studies were undertaken to determine by the newer techniques available what effect the single variable of increased renal venous pressure has on renal function.

METHODS

Twenty-two male or female dogs weighing 10 to 32 kg were used. They were anesthetized with sodium pentobarbital administered intravenously in doses of 30 to 35 mg/kg. Renal function was measured separately and simultaneously in the two kidneys by means of clearance techniques. During the experiment the pressure was raised only in the left renal vein. The right kidney thus served as a control.

Certain operative procedures were necessary to prepare the animal for study. The abdomen was opened by midline incision. Both ureters were cannulated with plastic tubing in order to collect urine from the two kidneys separately. The left renal venous pressure was measured with a saline manometer through a no. 9 or 10 venous catheter which had been inserted through a small incision into the right jugular vein and thence manipulated into the left renal vein. A constant infusion of isotonic saline solution flowed slowly through the catheter to prevent blockage by blood clot. The pressure in the left renal vein was raised by means of a specially constructed screw-clamp. Extension arms on the clamp made it possible to compress the renal vein and release the compression without disturbing the abdominal contents.

When the operative procedure was completed, urine was collected separately from the two kidneys during periods of equal duration ranging from 5 to 20 minutes. After two or three initial control periods the pressure in the left renal vein was raised by 50 to 420 mm. saline above the initial level which ranged around 100 mm. saline. The elevation in venous pressure was maintained for two to four periods. The clamp was then released and renal function studied for two or three additional periods at the control venous pressure. The mean arterial blood pressure was measured with a mercury manometer connected to the left common carotid artery. Left renal venous pressure and mean arterial blood pressure were recorded every 5 minutes.

The following clearance techniques were used. The creatinine clearance (CCr) was considered equivalent to the glomerular filtration rate and the clearance of para-
aminohippurate (C\text{PAH}) was considered an adequate estimate of renal plasma flow. Water excretion was recorded in some experiments as the percentage of filtrate excreted as urine, i.e. the urine flow divided by the filtration rate (V/C\text{F}). Sodium excretion has been treated similarly, the sodium clearance divided by the creatinine clearance (C\text{Na}/C\text{F}) giving the percentage of filtered sodium excreted in the urine. Therefore 1-C\text{Na}/C\text{F} is the percentage of filtered sodium reabsorbed. Glucose Tm(T\text{mo}) and diodrast Tm(T\text{md}) were measured in 2 dogs to evaluate tubular function.

With few exceptions each dog received during the operative procedure an amount of 1.5 or 2.0 per cent saline solution equal to 5 per cent of its body weight. This infusion was given in about 30 minutes to one hour through a cannula inserted into the right femoral vein and was followed by the administration of appropriate doses of creatinine, para-amino-hippurate (PAH), glucose or diodrast to attain blood concentrations within a suitable range, viz. 20 to 40 mg. per cent, 0.8 to 2.5 mg. per cent, 450 to 950 mg. per cent and 20 to 50 mg. per cent, respectively. These concentrations were maintained at a relatively stable level by the administration of a sustaining infusion at a constant rate of 2.7 to 3.0 cc. per minute. The amounts of the drugs for the initial dose and the infusion were calculated on the basis of the weight of each dog. Fifteen or 20 minutes after starting the sustaining infusion or after the last surgical manipulation, depending on whichever came later, the collection of urine samples was begun. Eight to 15 cc. of blood were withdrawn every 15 to 30 minutes through a retention needle inserted into the right femoral artery. Potassium oxalate was used as an anticoagulant. Blood samples were centrifuged and the plasma separated. Creatinine, PAH, glucose and diodrast were determined in plasma filtrates made with CdSO\text{4} according to the method of Fujita and Iwatake (19). Urine samples were collected directly in graduated cylinders and prepared for analysis by suitable dilutions. Creatinine was determined by a modification of Bonsnes's method (20), PAH by the method described by Goldring and Chasis (21), glucose by the Nelson-Somogyi method (22) and diodrast by Alpert's method (23), modified in this laboratory by Fithian and Baker (24). Sodium analyses were carried out on an internal standard type flame photometer.

RESULTS

The 13 dogs in which experimental procedures were satisfactory have been divided into 4 groups. In Group I were those dogs in which venous pressure was

4 In dog 26 no sodium was administered; both initial and sustaining infusions consisted of a solution of 10% dextrose in water. In dog 23 the amounts of water and sodium administered were limited. The initial infusion was an amount of 0.85% saline solution equal to 3% of the body weight and the sustaining infusion, likewise isotonic saline solution, was given at a rate of 2.6 cc/min. In dogs 22 and 27 glucose Tm and in dog 27 diodrast Tm were determined. These dogs received initially an amount of isotonic saline solution equal to 8 to 10% of body weight. The sustaining infusion of isotonic saline solution, which contained 15% glucose and 1.8% diodrast, was administered at a rate of 5 to 6 cc/min.

5 Clearance values were obtained on 22 dogs but the results in 7 were not considered valid because the filtration rate fell off more than 25% during the course of the experiment. The mean arterial blood pressure also gradually declined, usually to below 100 mm. Hg. Glucose Tm was determined in 2 of the 15 satisfactory experiments. The control values for C\text{PAH}, C\text{F} and filtration fraction per square meter of surface area were somewhat higher than those obtained by Selkurt (25)
raised to between 100 to 200 mm. saline, in Group II those in which venous pressure was raised to between 200 to 300 mm. saline and so on. With three exceptions the initial pressure was 100 ± 20 mm. saline. It has been assumed that the control pressure in the right renal vein was approximately the same as the control pressure in the left. The classification of the experiments into these 4 groups has been maintained throughout the presentation of the data in figures 1 through 6. In these figures the abscissa is divided into three sections. The first comprises the three control periods of urine collection at the initial venous pressure of 80 to 120 mm. saline. The second section contains five segments, each representing a different increment in venous pressure. Each of the five segments is subdivided into the three separate, successive periods of urine collection obtained while the venous pressure was elevated. Hence, it is possible to illustrate the effect on renal function of the duration of the increase in venous pressure as well as the effect of the height of the venous pressure. The third, or recovery section, comprises the three periods of urine collection following return of the left renal vein pressure to its control value. The results observed in any one dog will fall into the control section, one of the five segments of the increased venous pressure section, and into the recovery section. On the ordinate in all six figures are plotted the values which represent the function of the left kidney as compared to that of the right. The values representing the relative function of the left kidney are not the actual value differences between the two kidneys but are the percentages that the function in the left kidney differed from the same function in the right. For example, if the plasma flow through the left kidney was 105 cc/min. and that through the right kidney was 100 cc/min., the value plotted on the ordinate would be 105 X 100 or 105 per cent. The horizontal dotted lines in the figures indicate the values ± twice the standard deviation of the mean of the control values. It is to be noted that during the three control periods of urine collection the function of the left kidney did not deviate from that of the right by more than ±10 per cent, i.e. the function of the left was 90 to 110 per cent of that of the right. For this reason it has been assumed that any deviation of much more than 10 per cent during a period of increased venous pressure may be considered a significant deviation and attributable to the increased pressure in the left renal vein.

Effect of Increased Renal Venous Pressure on Renal Plasma Flow, Glomerular Filtration Rate and Filtration Fraction. Para-aminohippurate clearance (C_{PAH}) was measured in 10 dogs (fig. 1). Of these, 6 dogs showed no significant alteration of renal plasma flow through the left kidney despite elevation of the venous pressure up to 350 mm. saline for as long as 52 minutes. In 2 dogs C_{PAH} fell initially in the left kidney but only to a minimally significant extent and rose to control values again before the venous pressure was brought back to the control level. In 2 dogs (9 and 10), when the venous pressure was raised to 550 mm. saline, there was no initial fall in C_{PAH} but, after 15 to 20 minutes at that pressure, there was a significant drop in left renal plasma flow, 22 per cent and 66 per cent in dogs 10 and 9 respectively.

Glomerular filtration rate (C_{Cr}) was likewise essentially uninfluenced by elevation of the renal venous pressure up to 350 mm. saline (fig. 2). C_{Cr} fell slightly in
the left kidney in one dog (No. 5) in which the pressure in the left renal vein was maintained at 350 mm. saline for 52 minutes. There were significant decreases in glomerular filtration rate of 18 and 52 per cent respectively in dogs 10 and 9 in which the venous pressure was raised to 550 mm. saline.

The filtration fraction (F.F.) was not consistently altered by the elevation of the renal venous pressure until the venous pressure was raised to as high as 550 mm. saline. It was increased about 15 per cent in dog 9 and 5 per cent in dog 10. It is possible that a greater elevation of filtration fraction was masked by so-called ‘vicarious’ extraction of PAH by functioning nephrons from blood which had passed through the glomeruli of non-functioning nephrons.

Effect of Increased Renal Venous Pressure on Water and Sodium Excretion. In contrast to the lack of effect of moderate increases in venous pressure on renal plasma flow and filtration rate were the marked decreases in sodium and water excretion produced by only moderate elevation of renal venous pressure. This effect on urine flow (V, fig. 3) and sodium excretion (UVNa, fig. 4) was observed in one of two dogs, 23 and 25, when the venous pressure was raised to as little as 160 mm. saline. Further increments in venous pressure in other dogs decreased the excretion of water and sodium still more. In general the reduction of urine flow and sodium excretion tended to vary directly with the height of the venous pressure. Dog 13 constituted the only exception, the absence of significant effect on water and sodium excretion possibly being related to lack of parallel function between the two kidneys.

The depression of water and sodium output was either maintained throughout the periods of increased venous pressure or water and sodium loss became more marked with time, i.e. urine flow and sodium excretion from the left kidney continued to decrease throughout the three successive periods of increased venous pressure. Dog 24 was the only exception in this respect and for no apparent reason.

Following release of the clamp and return of the venous pressure to control levels the functions of the left kidney invariably returned toward control values although usually incompletely in the 10 to 20 minutes allotted. In no experiment was there a further decline in water or sodium excretion.

The changes in the percentages of filtered water and sodium excreted (V/Cr, fig. 5, and CSa/Cr, fig. 6, respectively) produced by moderate increases in renal venous pressure are further evidence that the reduction in water and sodium excretion occurred independently of minor fluctuations in the filtration rate. The marked decreases in the percentages of filtered water and sodium excreted which occurred when the venous pressure was raised to above 200 mm. saline also indicate that increased percentages of filtered water and sodium were reabsorbed.

The complete data of a typical experiment are given in table 1. Elevation of the pressure in the left renal vein to 340 mm. saline caused no significant reduction in either renal plasma flow or glomerular filtration rate in the left kidney but the urine flow and the amount of sodium excreted fell markedly during the 27 minutes that the renal venous pressure was kept elevated. The figure for percentage of filtered sodium reabsorbed is considered accurate to within ±1 per cent. Hence, during the time when venous pressure was elevated the difference of 3 per cent between the values for the two kidneys in the third period indicates that there was a significant increase in the rate of sodium reabsorption. Since, in this experiment, there was no
correlation between the percentage of sodium load reabsorbed and the magnitude of the load, it is concluded that the relative increase of 3 per cent in the left kidney was a result of the heightened pressure in the left renal vein.

<table>
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<th>CONTROL</th>
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<th>RECOVERY</th>
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<td>% CONTROL</td>
<td>(ML/100G X 100)</td>
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</tr>
<tr>
<td>PERIOD</td>
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<td>1 2 3</td>
</tr>
<tr>
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<td>100-200</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>PERIOD</td>
<td>1 2 3</td>
<td>1 2 3</td>
</tr>
<tr>
<td>V. P.</td>
<td>80-120</td>
<td>100-200</td>
</tr>
<tr>
<td>FILTRATION RATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERIOD</td>
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<td>1 2 3</td>
</tr>
<tr>
<td>V. P.</td>
<td>80-120</td>
<td>100-200</td>
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</table>

Fig. 1. EFFECT OF INCREASED VENOUS PRESSURE ON RENAL PLASMA FLOW. No significant depression of plasma flow occurred until the venous pressure was elevated to between 500-600 mm. saline.

Fig. 2. EFFECT OF INCREASED VENOUS PRESSURE ON GLOMERULAR FILTRATION RATE. No significant depression occurred with venous pressure elevated up to 350 mm. saline. Reduction in filtration rate did occur in a dogs at 550 mm. saline pressure.

The sodium load in 11 of the 13 experiments was raised above normal by the infusion of 1.5 or 2.0 per cent saline solution. In dog 24 the infusion was isotonic saline solution and in one other (dog 26) it was 10 per cent dextrose in water. In
these 2 dogs in which the sodium load was normal and below normal respectively (serum sodium was 127 mEq/l. in dog 26) the percentage changes in decreased water

and sodium excreted were comparable to those observed in the other dogs. In dog 26 the actual decrease in sodium excretion was, of course, much smaller.

Glucose Tm was measured in 2 dogs and diodrast Tm simultaneously in one of these (table 2). In both dogs there was a decrease in urine flow during elevation of the venous pressure without any significant change in glucose Tm or diodrast Tm.
DISCUSSION

By means of the techniques employed, it was demonstrated that elevation of the renal venous pressure from a mean normal of 100 mm. saline up to 340 mm. saline had no significant effect on renal plasma flow or glomerular filtration rate. Mean arterial blood pressure also remained essentially the same throughout the course of each study. Hence, elevation of the pressure in the left renal vein decreased the

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**Fig. 5.** Effect of increased venous pressure on percentage of filtrate excreted as urine, i.e., the percentage of filtered water excreted. At venous pressures above 200 mm. saline, there was depression of the percentage of filtered water excreted. This indicates that an increased percentage of filtered water was reabsorbed.

**Fig. 6.** Effect of increased venous pressure on percentage of filtered sodium excreted. The results are comparable to those obtained on the percentage of filtered water excreted. This indicates that an increased percentage of filtered sodium was reabsorbed.
pressure gradient from renal artery to vein. The constant plasma flow in the presence of a decreased pressure gradient implies a fall in the resistance within the renal circuit. Since there was no change in filtration rate or filtration fraction, the fall in resistance probably occurred distal to the glomerulus in the efferent arteriole and/or the peritubular capillary bed.

Table I. Results obtained in dog 12, 20.5 kg. female

<table>
<thead>
<tr>
<th>PERIOD</th>
<th>V</th>
<th>CREATININE</th>
<th>PAN</th>
<th>F.F.</th>
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<tr>
<td></td>
<td>R</td>
<td>L</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>mm. sal.</td>
<td>cc/min.</td>
<td>mg. %</td>
<td>mg. %</td>
<td>cc/min.</td>
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<tr>
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<td></td>
<td></td>
<td>3.12</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>2.27</td>
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</table>

1 Percentage of filtered sodium excreted. 2 Filtered sodium (sodium load). Uncorrected for Donnan equilibrium. 3 Excreted sodium. 4 Percentage of filtered sodium reabsorbed. V represents urine flow; U represents urine concentration; P represents plasma concentration 2 minutes prior to the midpoint of the urine collection period; UV/P represents clearance. F.F. is filtration fraction.

When venous pressure was raised to 550 mm. saline the renal plasma flow and glomerular filtration rate were reduced. In these experiments the decreased resistance in the post-glomerular circuit was presumably insufficient to compensate for the fall in pressure gradient and the renal plasma flow decreased. The increased filtration fraction observed in these experiments indicated that a significant degree
of back pressure extended proximal to the efferent arteriole and thereby increased effective filtration pressure. Regardless of the exact quantitative hemodynamic relationships involved, it seems most probable that significant peritubular capillary congestion did occur.

The effect observed on water and sodium excretion is in contrast to that on plasma flow and filtration rate. In one dog elevation of the renal venous pressure to only 160 mm. saline resulted in an appreciable decrease in urine flow and sodium excretion. With more marked increases in renal venous pressure the effect was more pronounced. The decreased excretion of water and sodium without concomitant reduction in filtration rate indicates an increased rate of water and sodium reabsorp-

<p>| Table 2. Effect of increased venous pressure (V.P.) on urine flow (V), filtration rate (C_G), glucose Tm (TmG), and diodrast Tm (TmD) |
|---|---|---|---|---|</p>
<table>
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<th>C_G</th>
<th>TmG</th>
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<td>136 128</td>
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The minor fluctuations encountered in measured filtration rate may be the result of certain technical shortcomings and/or possibly variability in the number of functioning nephrons. To minimize the influence of these minor fluctuations on the observed changes in sodium excretion the sodium to creatinine clearance ratio has been calculated for each urine-collection period. Water excretion has been handled similarly. The values for these ratios (V/C_G and C_Na/C_G, the percentages of filtered water and sodium excreted respectively) were also decreased by increased venous pressure, thus indicating again an increase in the percentages of filtered water and sodium reabsorbed. It might be worthwhile to point out that although small percentile changes in filtration rate may cause greater percentile
changes in \( U V_{Na} \) and hence influence \( C_{Na}/C_{Cr} \), this explanation cannot be invoked to invalidate the interpretation of the results. It is apparent from figure 2 that during the periods of increased venous pressure the filtration rate in the left kidney was greater than that in the right as often as it was smaller. Nevertheless, with one exception, there always was observed a decrease in urine volume and excreted sodium. It seems highly unlikely that the consistent decreases in urine volume and excreted sodium in the left kidney can be ascribed to a decrease in the glomerular filtration rate.

In general, the diminution in sodium and water excreted was progressive with time and was related to the height to which the pressure in the renal vein was raised. In only one dog did a return toward the control values occur prior to returning the venous pressure to the control level. In no experiment was renal venous pressure kept up for more than 52 minutes. Therefore, it is impossible to say whether or not chronic elevation of the venous pressure would lead to chronic retention of water and sodium and other possible secondary effects such as decreased renal plasma flow and glomerular filtration rate. But, regardless of what happens to renal plasma flow and glomerular filtration rate and regardless of the mechanism involved in the decreased excretion of sodium, the important fact remains that under the stated conditions the increased venous pressure did cause a significant retention of water and sodium.

The mechanism involved in the increased reabsorption of water and sodium as a result of increased renal venous pressure is not apparent. The effect was immediate and local, i.e. limited to the kidney in which the venous pressure was raised. This seems to eliminate as a cause any humoral or central reflex mechanism. It seems probable that the effect was mechanical rather than due to any specific alteration of the intrinsic physiology of the tubular cells. The lack of change in glucose Tm or diodrast Tm tends to support this conclusion. There is no definitive evidence to indicate whether the increased reabsorption of water was independent of or dependent on the increased reabsorption of sodium or vice versa. It is possible that the peritubular capillary congestion was responsible for the increased water and sodium reabsorption either by partially obstructing the flow of urine through the tubules or by increasing the time and capillary surface area available for transfer of water and sodium.

It is impossible to say whether or not the results obtained in acute experiments on anesthetized dogs have any bearing on the pathogenesis of edema in clinical cardiac failure. Certainly the increase in renal venous pressure necessary in our studies to produce a decrease in sodium and water excretion is well within the range of venous pressures found in frank cardiac failure or even before frank cardiac failure, during exertion. Hence, the rise of venous pressure occurring in cardiac failure may very well be a factor contributing to the formation of edema in cardiac failure. The possible rôle played by the increase in venous pressure in the formation of cardiac edema does not detract from the rôle played by the reduction in renal blood flow and filtration rate in the excretion of water and sodium. However, the factor of decreased renal blood flow and glomerular filtration rate \((10, 11)\) has been claimed to be responsible for the decreased excretion of sodium and water in cardiac failure, although the retention of sodium and water can be explained in our experiments on the basis of increased renal venous pressure alone. In terms of the Starling law of the heart,
the reduction in cardiac output occurs later in the development of cardiac failure than
the increase in right ventricular pressure. In other words, the cardiac output is
maintained at a normal level, everything else being equal, because the heart contains
more residual blood at the end of diastole. One may wonder if the increase in the
intraventricular pressure does not lead ultimately to an increase of the renal venous
pressure before a decrease in cardiac output occurs.

In short, it is probable that reduction in renal blood flow and filtration rate as
well as the increase in renal venous pressure plays a rôle in the formation of the edema
of cardiac failure. However, the causal and temporal relationship of these two
factors in the formation of cardiac edema and their relative importance remain
uncertain.

SUMMARY

The effect of increased renal venous pressure on renal function was studied in
anesthetized dogs by means of clearance techniques. Renal function was measured
separately and simultaneously in the two kidneys but the pressure was raised in the
left renal vein only, by means of a specially designed clamp. Venous pressure was
measured with a saline manometer through a venous catheter which had been passed
into the left renal vein. Control values for the functions of the left kidney were
obtained before and after elevation of venous pressure and were comparable to con-
trols obtained from the right kidney. Under the stated conditions moderate eleva-
tion of the left renal venous pressure up to 350 mm. saline caused in that kidney a
significant decrease in water and sodium excretion without any change in the renal
plasma flow, glomerular filtration rate, glucose Tm or diodrast Tm. The reduction
in water and sodium excretion was due to an increase in the reabsorption rate of these
substances by the renal tubule cells. This effect also occurred when the sodium load
was low, for example in one experiment in which the serum sodium was 127 MEq/l.
Greater elevation of venous pressure to 550 mm. saline decreased renal blood flow and
filtration rate, but the results were not sufficient to state whether filtration fraction
was significantly altered.

The mechanism for the increased reabsorption of sodium and water ascribed to
increased venous pressure was not obvious. It was local, i.e. confined to the kidney
in which the venous pressure was raised and consequently was not related to release
of pituitary, adrenal and hepatic hormones. It probably was mechanical rather
than the result of any alteration in specific metabolic processes of the tubular cells
since there were no associated changes in glucose Tm or diodrast Tm. Some of the
implications of these results with respect to the pathogenesis of edema in cardiac
failure have been discussed.

REFERENCES

Venous pressure and renal function


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