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THE INFLUENCE OF HEPATIC PORTAL CIRCULATION ON URINE FLOW

By C. C. LIANG

From the Department of Physiology, University of Hong Kong, Hong Kong

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SUMMARY

1. A study of the effect of changes in the hepatic portal venous pressure (HPVP) on the rate of urine flow in dogs has been made. Normally this pressure varies between 3·7 and 14·9 cm H_2O. It can be raised or lowered by varying the method of manipulation of the visceral organs.

2. When the HPVP was raised within 15 cm H_2O above the pre-manipulation level it caused an increase in urine flow to 2–3 times the normal levels within 2–5 sec. If the HPVP was raised to more than 15 cm H_2O above the pre-manipulation levels it resulted in a period of anti-diuresis. The urine flow returned rapidly to normal level immediately after the pressure was released.

3. The kidney volume increased when an induced diuresis occurred and decreased when an antidiuresis occurred.

4. The urine chloride concentration decreased during diuresis, but total chloride excretion increased. Total chloride excretion was reduced when an antidiuresis occurred.

5. Topical application of local anaesthetics at the hilus of the kidney and on the renal nervous plexus abolished the response. This and other evidence indicate that this effect on urine flow is a result of nervous reflex activity, probably involving the sympathetic but not the vagus.

6. The receptive area lies in the mesentery between the mesenteric capillaries and the main portal vein.

INTRODUCTION

Chéruy, Lemarchands, Potocki, Reynier & Tanche (1962) and Potocki, Eteradossi, Lemarchands & Reynier (1964) observed that changes in the portal venous circulation could result in change in the renal circulation. The cause of the effect is a nervous mechanism. Ohm & Haberich (1969) have recently studied the hepatic portal venous pressure (HPVP) in the

unanaesthetized rat. They found that during the time of elevation of the HPVP there was an anuria; and lowering of the HPVP was accompanied by an increase of urine flow under the conditions of water and osmotic diuresis. They claimed that the existence of stretch receptors in the portal circulation could affect the urine flow either directly or via the release of antidiuretic hormone (ADH).

The present investigation attempts to establish how the HPVP could influence the renal blood flow through a nervous mechanism, which then causes an immediate change in urine flow.

METHODS

Dogs of either sex, weighing from 9 to 17 kg, were anaesthetized with pentobarbitone sodium (30 mg/kg) I.V. The trachea of each dog was exposed in the cervical region. The peritoneal cavity was opened by a mid line incision extending from the xiphisternal junction to a point about 5 cm from the symphysis pubis. A polyethylene cannula was inserted into each ureter just cephalic to the entry into the urinary bladder and secured by two ligatures. The flow of urine from one or both kidneys was recorded by a drop-recorder and the urine samples were collected into a series of graduated tubes at 1 min intervals. All infusions were given into a femoral vein through a polyethylene catheter pushed up through the vena cava to the level of the renal veins. This catheter was connected to a three-way tap, with one arm connected to a dripping bottle containing normal saline at an infusion rate of approximate 0·2 ml./min. kg body wt., the other arm to a mercury manometer for measurement of the femoral venous pressure.

Systemic arterial blood pressure was measured through a polyethylene tube in the femoral artery connected to a pressure transducer. Another polyethylene catheter for the measurement of the HPVP was introduced via a mesenteric vein and advanced until it reached the common mesenteric. This cannula was connected to a three-way tap with one arm connected to a saline reservoir and the other arm to a low-pressure transducer. The reservoir was first adjusted to zero level and then levelled with the transducer before turning to the cannula for the registration of HPVP. In some experiments the HPVP was varied by raising or lowering the reservoir.

A plethysmograph was applied on the left kidney and any change in the volume of the kidney was recorded through a pressure transducer.

All these transducers were connected to the proper channel of a Sanborn Multichannel physiograph, so that the changes in the volume of the kidney, the systemic arterial B.P., HPVP, and the rate of urine flow in drops could be recorded continuously on the same tracing paper.

Glass hooks were placed around the portal vein and on different places of the intestine or other visceral organs, so that by raising or lowering these hooks exteriorly one could distend or compress different organs or occlude different parts of the vessels in the viscera so as to change the HPVP. Some manipulations were done by hand, but unnecessary disturbances of the viscera were avoided. The intestine was returned into the abdominal cavity, and the abdomen was temporarily sutured in order to raise the intra-abdominal pressure by abdominal compression, when necessary.

In some experiments connective and fatty tissues from the hilar area of the left kidney were carefully removed, avoiding damage to the nerves. The hilar area was wrapped with cotton wool for the topical application of local anaesthetics, 5% xylocaine or 5% procaine. After the expected effect was observed, the cotton wool

was removed and the hilus washed several times with normal saline until normal activity was restored. The response of the right kidney was used as control in the same experiment. Local anaesthetics were also applied to the renal nervous plexus on the surface of the aorta and to the sympathetic chains of the inner abdominal wall including the splanchnic nerves.

Blood samples were collected from the right femoral artery before and during the manipulation. Determination of clearance values of PAH and creatinine to represent the RPF and GFR was conducted according to the methods of Selkurt (1947) and Bonsnes & Taussky (1945) respectively. A priming injection of creatinine (20 mg/kg) and sodium *p*-aminohippurate (5 mg/kg) was given I.V. followed by an I.V. sustaining infusion of 0·9 % NaCl containing creatinine, approximately 6 mg/kg, and sodium *p*-aminohippurate, 2 mg/ml. After 30 min to allow equilibrium, urine and blood samples were obtained. The arterial plasma concentration of creatinine was found to be 12–16 mg/100 ml. and of PAH 1·04–1·10 mg/100 ml. When an experimental intervention was made, the first 1·6 ml. urine from each kidney was not included in the determination, since it was found that, in all the dogs examined, the volume of urine trapped in the pelvis, ureter and the catheter from each kidney before the arrival of a new portion of urine, as a result of the manipulation, varied from 1·5 to 1·7 ml. (average 1·6 ml.). The remaining urine was carefully collected in separate tubes.

Extra blood samples were collected in heparinized, graduated centrifuge tubes and centrifuged for 15 min at 3000 rev/min to obtain their haematocrit values (Ht). Plasma and urine chloride concentrations were determined according to the method of Sendroy (1942). Plasma protein concentration was determined according to the method of Lowry, Rosebrough, Farr & Randall (1951).

RESULTS

The normal HPVP varied from 3·7 to 14·9 cm H_2O with an average of 8·7 cm H_2O (eighteen dogs). These values accord with those obtained by Winton (1931), Olerud (1953) and Torrance (1961). The HPVP undergoes fluctuation with respiration due to the movement of the diaphragm (McMichael, 1932). Occlusion of the mesenteric artery reduced the HPVP, indicating that under normal condition the driving force of the portal blood is *vis a tergo* from the mesenteric artery. The HPVP could be raised by various manipulations, such as stretching or pressing the small and large intestines or the stomach. It could also be varied by partial or complete occlusion of the main hepatic portal vein, compression of the abdominal wall, infusion of saline of different concentrations into the mesenteric veins, or administration of water or saline into the stomach or small intestine.

In all these manipulations, when the HPVP was raised to values less than 15 cm H_2O above the pre-manipulation level, there occurred an increased rate of urine flow which was sometimes trifling but sometimes very large (Fig. 1). The urine flow rate bore no obvious relationship to the magnitude of the increased HPVP, except that raising the HPVP by more than 15 cm H_2O above the pre-manipulation level was often followed by

a decrease or a complete cessation of urine flow. This diuresis or antidiuresis appeared within 2–5 sec after the change in the HPVP and quickly returned to the normal value when the HPVP fell to normal levels. However, in two out of eighteen dogs examined, antidiuresis was the only response obtained from all kinds of handlings (Fig. 1).

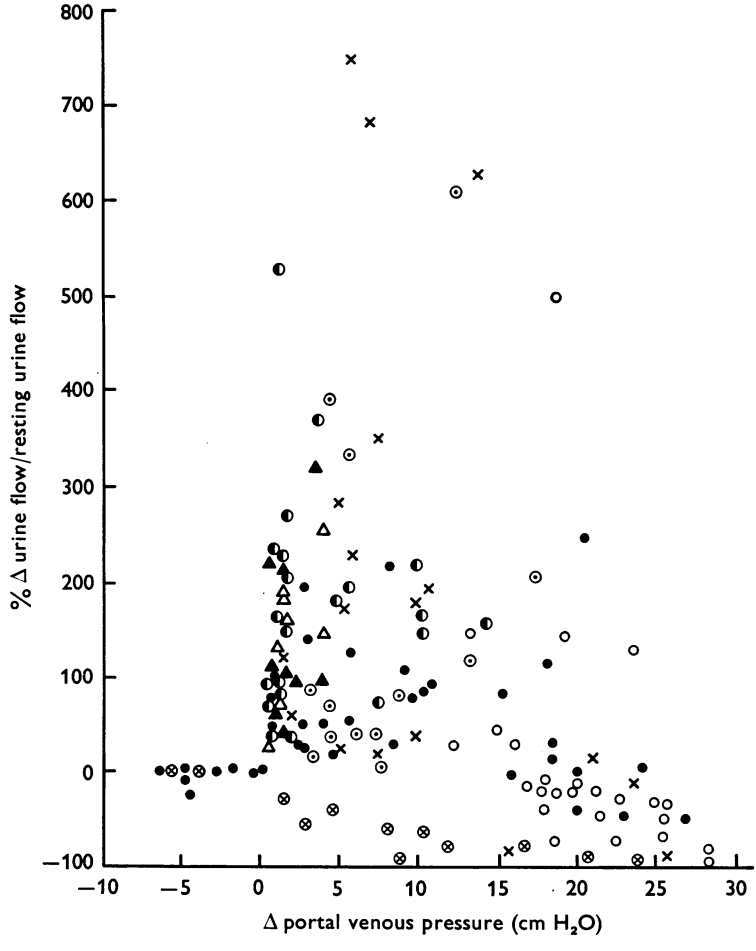

Fig. 1. Effect on urine flow of change in HPVP resulting from different manipulations. Abscissa: difference in HPVP from the pre-manipulation level. Ordinate: percentage of difference in the urine flow. ●, Infusion of normal saline into the mesenteric vein; ○, compression of abdominal wall; ×, occlusion of the main hepatic portal vein; ◐, distension of small intestine; △, administration of normal saline into small intestine; ▲, administration of normal saline into stomach; ⊙, infusion of 0·5 and 2·0% saline into the mesenteric vein, at HPVP = 9·5 cm H_2O. ⊗, those values from the two dogs where antidiuretic changes only occurred.

When the HPVP was decreased by occlusion of the mesenteric artery or by lowering the saline reservoir connecting the catheter to the mesenteric veins, there was practically no change in the urine flow (Figs. 1 and 2).

Since dogs under experiment were placed in a supine position on the dog table, the venous pressure in the femoral vein or the vena cava near the exit of the renal veins can be considered as a close approximation of the renal venous pressure (Gomez, 1951); it ranged between 4 and 12 mm Hg with an average value of 8 mm Hg. This venous pressure stayed fairly

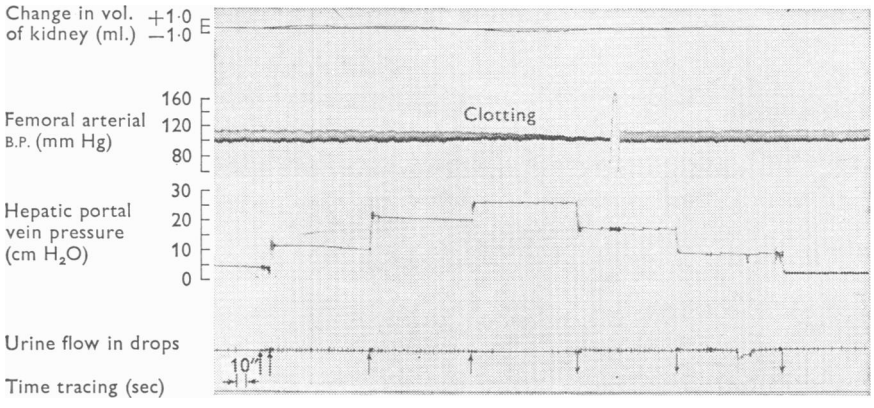

Fig. 2. Effect on urine flow of changing the HPVP by raising or lowering the reservoir. First arrow indicates the disturbance by handling the small intestine. The next three upward arrows indicate successive raisings of the HPVP. The three downward arrows indicate the successive lowerings of the HPVP. When the HPVP fell to a level lower than the normal HPVP, there was no change in the urine flow.

constant in most cases in the course of manipulation. The mesenteric arterial B.P. may fluctuate with change of the systemic B.P., but it did not affect the mesenteric venous pressure or the HPVP. This observation has been reported earlier by Gammon & Bronk (1935).

According to the plethysmographic measurements, whenever a diuresis occurred there was an increased volume of the kidney; an antidiuresis was always accompanied by decreased volume of the kidney. The volume of each kidney was found to vary from 23 to 34 ml., the change in volume resulting from manipulations being within the range $\pm 2{\cdot}0\,\%$ of the normal kidney volume. The changes in kidney volume seemed to be associated with the increased or decreased RBF to be noted below.

When a diuresis occurred, C_{PAH} increased from control values of 310–330 ml./min. 100 g kidney to values up to 1140 ml./min. 100 g kidney; and C_{CR} from a mean control value of 71 ml./min. 100 g kidney to as high as 121 ml./min. 100 g kidney. The relative changes in C_{PAH} and C_{CR} were

such that filtration fraction (F) usually fell. Conversely, when an antidiuresis occurred, C_{PAH} fell but F increased. The changes in RBF, GFR and urine flow are summarized in Fig. 3.

During diuresis, the urine chloride concentration decreased. Since the total volume of urine excreted in the same period was greater than the normal level, the total chloride excretion increased. Conversely, chloride output fell when an antidiuresis occurred (Fig. 4).

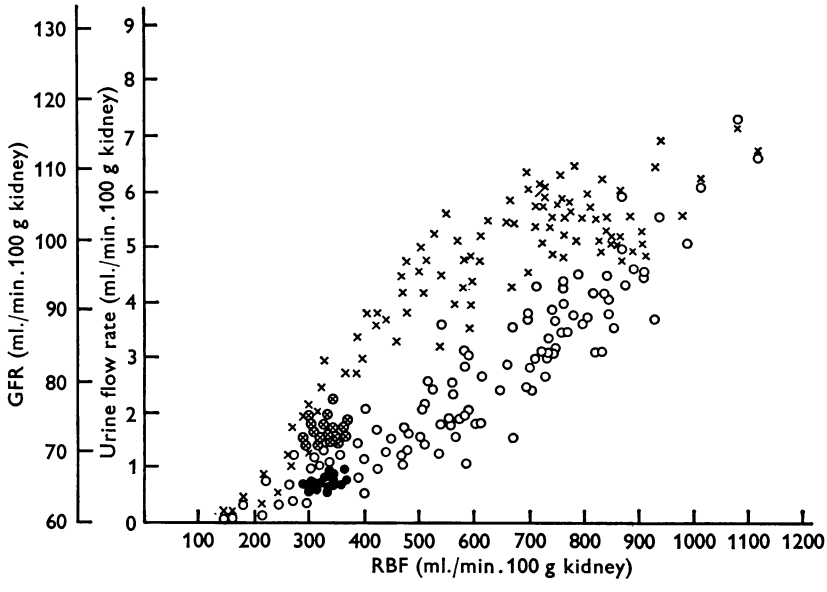

Fig. 3. Plot of RBF against urine flow, ● normal, ○ manipulation; and against GFR, ⊗ normal, × manipulation.

Vagotomy performed in the course of different manipulations did not affect the rate of urine flow. After vagotomy weak electrical stimulation of the distal end of either vagus caused an increased intestinal peristalsis and secondarily caused a fluctuation of the HPVP and thus indirectly induced diuresis.

Topical application of local anaesthetics (xylocaine or procaine) on the pedicle of one kidney, using the other kidney as the control, showed that this kidney gradually lost its response (Fig. 5), while the untreated kidney responded normally to the changes in HPVP with changes in urine flow. Washing out the local anaesthetic promptly restored the response. Topical application of local anaesthetic to the renal nervous plexus on the surface of the aorta also abolished the renal response. Blocking by local anaesthetic further up on the sympathetic chain and on the splanchnic nerves had no effect.

A slight increase in HPVP followed the infusion of hypotonic, isotonic

or hypertonic saline into the small intestine and stomach. These induced a rapid change in urine flow which lasted as long as the pressure remained at a higher level.

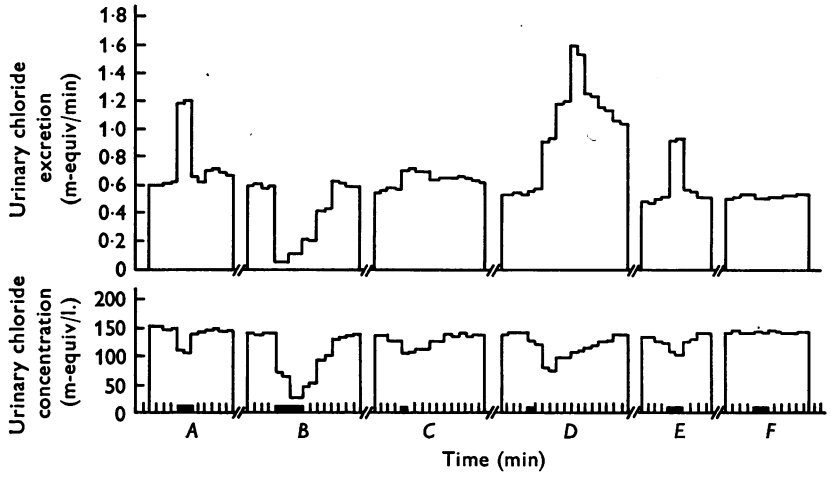

Fig. 4. Effect of different manipulations on urinary chloride concentration and chloride excretion. Bars denote duration of the manipulation. *A*, compress the abdominal wall with HPVP at 11·7 cm H_2O; *B*, compress the abdominal wall HPVP at 19·3 cm H_2O; *C*, administration of normal saline into stomach; *D*, administration of normal saline into intestine; *E*, distension of small intestine; *F*, decrease HPVP to 1·0 cm. H_2O by lowering the reservoir.

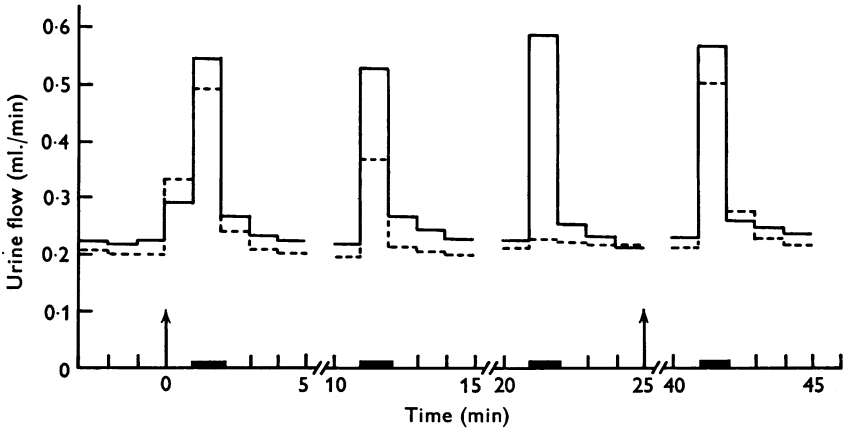

Fig. 5. Effect of topical application of xylocaine to the hilar area of the left kidney (dashed line) on the changes in urine flow induced by compressing the abdominal wall. The right kidney was used as a control (continuous line). First arrow indicates the application and the second arrow indicates the washing out of the local anaesthetic. Bars indicate periods of abdominal compression.

DISCUSSION

As mentioned in the Introduction, recent studies (e.g. Chéruy *et al.* 1962; Potocki *et al.* 1964) have demonstrated that visceral organs may influence renal function. However, both the physiological significance and the mechanisms involved are uncertain. Milies (1960) suggested that a humoral diuretic factor might be liberated by the liver. Haberich (1968) suggested that urine flow might be influenced by a nervous reflex mechanism, initiated by stimulation of osmoreceptors within the hepatic portal circulation. More recently, it has been postulated that stimulation of stretch receptors in the portal circulation might affect urine flow either directly by a nervous reflex mechanism, or by influencing release of ADH (Ohm & Haberich, 1969).

If humoral mechanisms were involved in the effects described here, the response time would be expected to be much longer than was found. The immediate onset and immediate withdrawal (both within seconds) of the urinary response to changes in HPVP suggests that a nervous reflex mechanism is involved.

The effective stimulus to such reflex responses is unlikely to be related to blood pressure in either the systemic or mesenteric arterial systems: diuresis occurred on occasions when B.P. increased, fell or remained unaltered, while B.P. in the mesenteric artery fluctuated with systemic arterial B.P. It is more likely, therefore, that changes in mesenteric or portal venous pressure were responsible. Whether the abundant mesenteric Pacinian corpuscles (e.g. Gammon & Bronk, 1935; Heymans & Neil, 1958) could act as the appropriate stretch receptors is unknown.

Neither vagotomy nor blockage on the sympathetic chain abolished the response, whereas topical application of local anaesthetics at the renal nervous plexus did so. It is concluded that the nervous reflex pathway involved the sympathetic but not the vagus; this is compatible with the rich sympathetic innervation of the kidney (e.g. Mitchell, 1950).

The mechanisms by which such changes in nervous reflex activity may have caused the changes in urinary flow are also uncertain, but the accompanying effects on C_{PAH} and C_{CR} are compatible with the view that changes in renal haemodynamics occurred and that these were induced by renal vasomotor regulatory mechanisms. Furthermore, the effect on filtration fraction (F) suggest that changes in arteriolar resistance may have occurred.

Although C_{PAH} has been regarded as a measure of renal blood flow, complete extraction of PAH is accomplished only by the renal cortex (see review by Thurau, 1964). Interpretation of changes in C_{PAH} is complicated, therefore, by the possibility that differences in the cortical distribution of

blood may accompany the non-uniformity of nephrons (Flohr, 1969); and redistribution of blood flow between cortical and medullary circulations has been described in various circumstances (e.g. Pomeranz, Birtch & Barger, 1968). In this respect, a reduction in the renal extraction of PAH (E_{PAH}) during adrenaline infusion in dogs has been interpreted as resulting from a reduction in cortical blood flow (Pilkington, Binder, de Haas & Pitts, 1965); and renal nerve stimulation has been reported to reduce E_{PAH} (Gömöri, Földi & Szabo, 1961). However, there is some inconsistency in the literature concerning the results of similar studies on E_{PAH} and approximately similar relative changes in cortical and medullary blood flow have been reported by other workers, using other methods, in various circumstances (e.g. Aukland, 1968). For these reasons, a more precise interpretation of the changes in renal haemodynamics reported here must await further work.

Similarly, the extent to which the changes in chloride excretion are directly attributable to nervous mechanisms or indirect consequences of altered renal haemodynamics is also uncertain. Reabsorption of NaCl may be influenced by adrenergic mechanisms (e.g. Pomeranz *et al.* 1968). However, it has been proposed that the changes in NaCl reabsorption associated with altered total renal blood flow and with redistribution of cortical and medullary blood flow may be caused by the changes in peritubular, physical factors (e.g. Earley & Friedler, 1965; see review by Earley & Daugharty, 1969).

In summary, the present report describes changes in urinary flow and chloride excretion in response to various manipulations of visceral organs. The rapidity of these responses and the results of nerve blocking indicate that nervous reflex mechanisms are involved. It may be speculated that such a nervous reflex mechanism may participate in other circumstances. The results of further studies will appear in subsequent reports.

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Note added in proof

Since the submission of this report, Schneider, Davis, Robb, Baumber, Johnson & Wright (1970) found no evidence for an osmoreceptor mechanism (Haberich, 1968) in the liver of the dog. A low perfusion rate into the hepatic portal vein did not induce a diuretic or natriuretic response, but a faster rate of perfusion rate did. This increased rate of perfusion would be expected to increase the HPVP and thus might induce the same response mentioned in this paper.

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