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EFFECT OF NORADRENALINE ON URINE AND RENAL BLOOD FLOW

BY

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In six human subjects, noradrenaline infusions of 32–44 μg./min. produced albuminuria, and an average reduction of renal plasma flow, glomerular filtration rate, and urine flow to 43%, 62%, and 43% of control values respectively (King and Baldwin, 1956). The highest blood pressure recorded in these experiments was 204 mm. Hg systolic and 118 mm. Hg diastolic.

Despite the marked changes induced, this dose of noradrenaline is sometimes exceeded therapeutically; it is also much exceeded during the crises from a phaeochromocytoma. It thus becomes of interest to know the extent of the reduction in renal blood flow that may occur when noradrenaline is administered in doses sufficient either to restore the blood pressure in shock, or to raise it to levels comparable with those occurring during the crises from a phaeochromocytoma.

These problems have been investigated in dogs, because the necessary observations cannot be made in man in the presence of anuria or marked oliguria which necessitates measurement of renal blood flow by direct means. A résumé of this work was read to the Belgian Physiological Society on April 21, 1956 (Marson, 1956).

METHODS

Arterial blood pressure was recorded with a mercury manometer from the left femoral artery of dogs which were anaesthetized with chloralosane (110–120 mg./kg.); all measurements refer to systolic readings. Normal saline was infused at a rate constant for any one experiment into the left femoral vein. A freshly prepared solution of (±)-noradrenaline HCl was infused into the right femoral vein. The weights of noradrenaline are expressed in terms of the hydrochloride.

Study of Urine Flow.—The abdomen was opened and catheters were inserted into the lower ends of both ureters. The catheters led into small measuring cylinders which were changed every few minutes. After urine started flowing into the cylinders, and after preliminary observations, noradrenaline was infused intermittently and at various rates.

Study of Renal Blood Flow.—After homotransplantation of both kidneys into the neck, renal blood flow was measured by the methods of Brull (1931) and of Dor and Brull (1940) in which it is necessary to use a large perfusing dog and a small donor dog, both receiving artificial respiration by a positive pressure machine. The common carotid artery and external jugular vein of the perfusing dog were first ligated and divided, and Payr's cannulae were inserted into the clamped caudal ends of these vessels. Bilateral adrenalectomies were performed and both kidneys were then removed from the donor dog together with a few inches of aorta and inferior vena cava both above and below the renal vessels. The cephalic ends of the aorta and the inferior vena cava of the donor dog were then anastomosed to the caudal ends of the common carotid artery and external jugular vein of the perfusing dog. The arterial anastomosis is facilitated by a similarity in size between the common carotid artery of the large perfusing dog and the aorta of the small donor dog. The renal circulation had to be stopped for 3–4 min. during the transplantation. The free end of the aorta remained ligated, and the clamped free end of the inferior vena cava was attached to a special 10 or 20 ml. pipette. Renal blood flow was measured by releasing the clamp on the inferior vena cava proximal to the pipette and occluding the return of blood from the kidneys through the external jugular vein. The time for the passage of blood between two marks on the pipette was measured.

In some experiments, measured volumes of blood were removed through a cannula in the right femoral artery; this blood, to which heparin was added, was later reinjected into the left femoral vein.

RESULTS

Effect of Noradrenaline on Urine Flow.—Fig. 1 illustrates the alterations in urine flow and blood pressure during an experiment in which noradrenaline was given on seven occasions. The dose of noradrenaline was 1.65–22.4 μg./kg./min., and the infusions were continued for 2–18 min. The beginning of infusion was accompanied by an abrupt fall in the rate of urine flow proportional to the dose of noradrenaline; anuria occurred on the

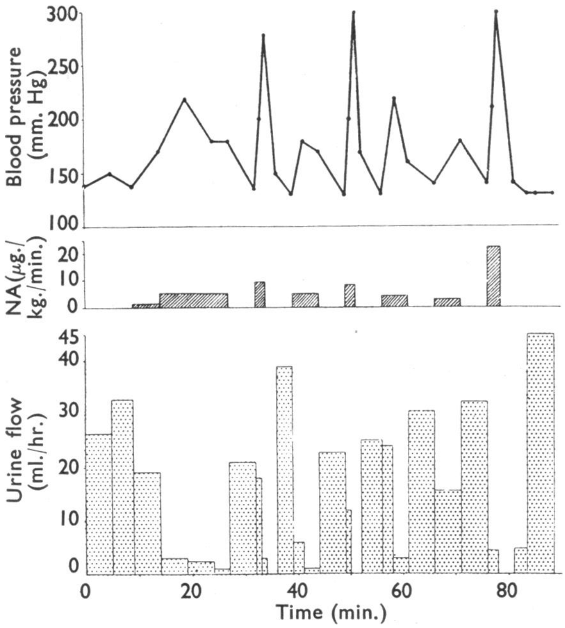

FIG. 1.—Dog, 14.9 kg., chloralosane 120 mg./kg. Showing the effect of intravenous noradrenaline (NA) on the urine flow and blood pressure.

three occasions on which the dose was 8.7 µg./kg./min. or higher.

Similar experiments were performed in twelve dogs. Noradrenaline always induced oliguria or anuria according to the dose. Table I shows the rates of noradrenaline infusion that produced anuria, together with the blood pressure at these times. The noradrenaline dose varied from 5.5–24.3 µg./kg./min.; the blood pressure was no higher than 200 mm. Hg in seven of the twelve experiments.

Anuria occurred within 15 sec. of the start of noradrenaline infusion. The urine flow always returned within 2 min. of stopping the infusion, often despite a marked temporary fall in blood pressure following withdrawal of the drug.

TABLE I

RATE OF NORADRENALINE INFUSION AT WHICH ANURIA OCCURRED

Wt. of Dog (kg.)	Noradrenaline (µg./kg./min.)	B.P. (mm. Hg)	
		Control	With Noradrenaline
10·3	7·45	165	200
12·4	12·4	150	200
3·5	13·2	130	200
14·9	15·4	180	230
10·0	16·2	120	240
7·5	8·6	165	190
13·3	24·3	160	210
12·0	9·6	135	220
16·7	5·5	185	190
14·9	8·7	180	300
9·1	6·1	185	200
24·9	10·5	160	180

Effect of Noradrenaline on the Blood Flow of Transplanted Kidneys.—Fig. 2 illustrates the changes in blood pressure and renal blood flow during six periods of noradrenaline infusion. In this experiment noradrenaline (1.4–3.7 µg./kg./min.) produced a prompt and marked fall in renal blood flow; when the noradrenaline dose was 4.6–13.8 µg./kg./min. the kidneys became very soft and pale, renal blood flow was completely arrested, and the blood pressure varied from 190 to 250 mm. Hg. On each occasion arrest of blood flow was observed for at least 2 min., but the flow always started again within half to one minute of stopping the noradrenaline. It was noticeable that the renal blood flow often recommenced 5–15 sec. before any fall in systemic blood pressure occurred, and that the rate of flow continued to increase despite a fall in blood pressure to below control levels.

Similar experiments were performed in five other dogs; Fig. 3 illustrates the changes in renal blood flow induced by various doses of noradrenaline. In any one experiment the degree of reduction in blood flow depended upon the dose of noradrenaline. Although the renal blood flow was not completely arrested in any of these further experiments, it was always reduced to below 14% of the control level. The graphs suggest that the rates of recovery of blood flow on stopping noradrenaline are partly dependent upon the duration of the noradrenaline infusion.

Alteration in Urine Flow Induced by Acute Haemorrhage and the Effect of Noradrenaline Before and After Reinjection of the Blood.—In one experiment (Fig. 4), removal of 450 ml. of blood (12.4 kg. dog) reduced the blood pressure from 180 to 100 mm. Hg. Anuria occurred at first and was followed by a slow urine flow. At this stage sufficient noradrenaline (8 µg./kg./min.) was given to restore the blood pressure to the original control level, and this was maintained for 20 min. Despite restoration of blood pressure, anuria persisted throughout the noradrenaline infusion. A slight urine flow returned 18 min. after stopping the infusion. After the reinjection of 200 ml. of blood a good diuresis occurred promptly, and was particularly marked for the first 5 min. A second 200 ml. blood produced a further diuresis. The dog having now received all but 50 ml. of the blood removed, noradrenaline was restarted. With an initial dose of 2 µg./kg./min. no reduction in urine flow occurred, but when the dose was raised

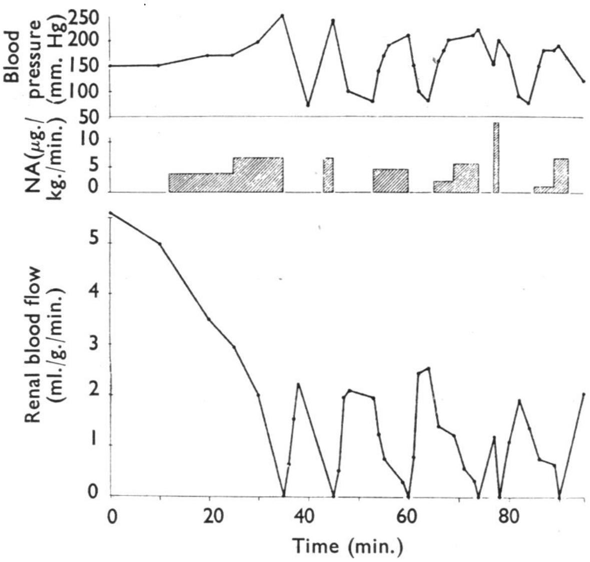

Fig. 2.—Dog, 26.7 kg., chloralosane 110 mg./kg. Showing the effect of intravenous noradrenaline (NA) on the blood flow of transplanted kidneys in the neck.

to 7.5 μg./kg./min. there was oliguria and the blood pressure rose above the control level. On stopping the noradrenaline there was a marked diuresis despite the fall in blood pressure to 100 mm. Hg, a level which, when induced by haemorrhage, had been accompanied by a great reduction in urine flow.

Similar experiments were carried out in four other dogs, and Table II shows the extent of the haemorrhage, its effect on blood pressure, and the dose of noradrenaline required to restore the blood pressure to the control level. Despite this correction, anuria occurred during the infusion in all but one dog in which oliguria was observed. A brisk and marked diuresis always occurred after stopping the noradrenaline and reinjecting the removed blood, this measure being accompanied by a return of the blood pressure either to the control level or slightly below it.

Effect of Noradrenaline on Renal Blood Flow During a Period of Acute Haemorrhage.—Fig. 5 illustrates the effect of acute haemorrhage on renal blood flow, removal of 225 ml. blood (13.5 kg. dog) having reduced the blood pressure from 115 to 35 mm. Hg with a spontaneous rise to 70 mm. Hg after 2 min. The renal blood flow fell from 2.1 to 0.6 ml./g./min. (29% of the con-

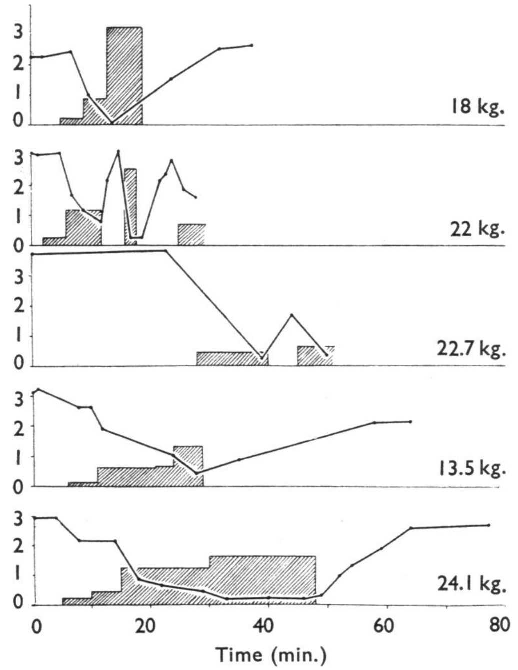

Fig. 3.—Five experiments showing the effect of intravenous noradrenaline (striped rectangles; × 10 μg./kg./min.) on renal blood flow (continuous lines; ml./g./min.). The dogs' weights are indicated.

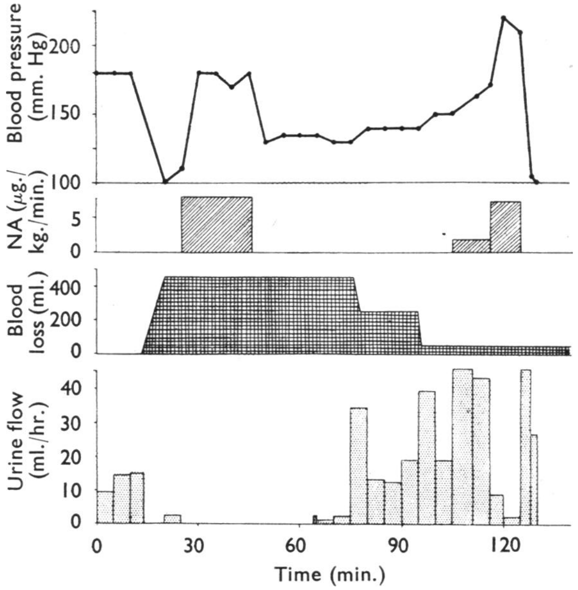

Fig. 4.—Dog, 12.4 kg., chloralosane 120 mg./kg. Showing the alteration in urine flow following acute haemorrhage, and the effect of noradrenaline (NA) before and after reinjection of the blood.

TABLE II

DOSE OF NORADRENALINE REQUIRED TO RESTORE BLOOD PRESSURE AFTER ACUTE HAEMORRHAGE

Anuria occurred in all but the fourth dog in which there was oliguria

Wt. of Dog (kg.)	Volume of Blood Removed (ml.)	B.P. (mm. Hg)		Noradrenaline (μg./kg./min.)
		Control	After Bleeding	
12·4	450	180	100	8·1
14·9	500	180	85	11·5
7·5	250	150	60	8·6
13·3	330	145	70	6·2
14·9	400	160	80	6·6

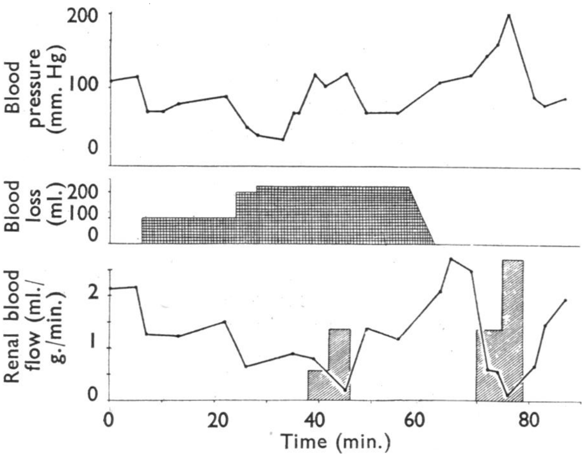

FIG. 5.—Dog, 13.5 kg., chloralosane 110 mg./kg. Showing the effect of intravenous noradrenaline (bottom section, striped rectangles; × 10 μg./kg./min.) on renal blood flow during haemorrhage and after restoration of the blood.

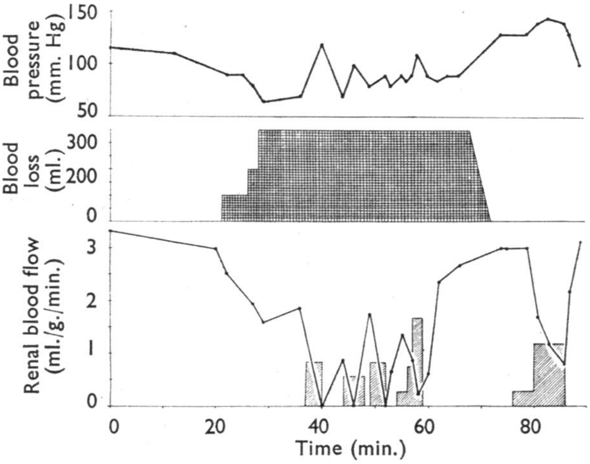

FIG. 6.—Dog, 22 kg., chloralosane 110 mg./kg. Showing the effect of intravenous noradrenaline (bottom section, striped rectangles; × 10 μg./kg./min.) on renal blood flow during acute haemorrhage and after restoration of the blood.

trol level). Noradrenaline (13.6 μg./kg./min.) then raised the blood pressure to 120 mm. Hg, but induced a further fall in renal blood flow to 0.19 ml./g./min. (9% of the control level). On stopping the noradrenaline and reinjecting the blood, the renal blood flow rapidly returned to the control level, but noradrenaline at the same rate again caused a marked reduction in renal blood flow. This reduction—to 0.6 ml./g./min.—was not so great as that before restoration of the blood, although further reduction in blood flow occurred on raising the noradrenaline dose.

Fig. 6 illustrates another similar experiment in which 350 ml. blood (22 kg. dog) was removed. Following this haemorrhage, the renal blood flow fell to approximately half the control level. Three separate infusions of noradrenaline (8.4, 5.6, and 8.4 μg./kg./min.) each caused complete arrest of renal blood flow, and simultaneously raised the blood pressure to 120, 100, and 90 mm. Hg respectively, the control levels before haemorrhage having been between 100 and 115 mm. Hg. A fourth infusion (up to 16.8 μg./kg./min.) greatly reduced the renal blood flow but did not arrest it. After stopping the infusion the blood pressure and renal blood flow were both appreciably higher than at the start of the blood loss, the recovery having occurred in 30 min. After restoration of the blood the effect of a further infusion of noradrenaline depressed the renal blood flow but not so much as before restoration.

Effect of Acute Haemorrhage, and of Noradrenaline, on Blood Flow and Urine Formation in Transplanted Kidneys.—Although only one experiment of this type was performed, the inclusion of observations on the rate of urine flow from the transplanted kidneys permitted a comprehensive study which incorporated many of the changes observed in the previous experiments. The results are illustrated in Fig. 7. The first infusion of noradrenaline was accompanied by a fall in renal blood flow from 3.68 to 1.81 ml./g./min. (49% of the control level), together with anuria. After removal of 560 ml. blood (18 kg. dog), the renal blood flow fell to 0.71 ml./g./min. (19.3% of the control level), and anuria occurred. During the blood loss, noradrenaline (9.2 μg./kg./min.) raised the blood pressure to the level preceding haemorrhage but decreased the renal blood flow still further to 0.18 ml./g./min. (4.8% of the control level). After stopping the noradrenaline and reinjecting the blood, the renal blood flow rose rapidly to 2.3 ml./g./min. and urine flowed

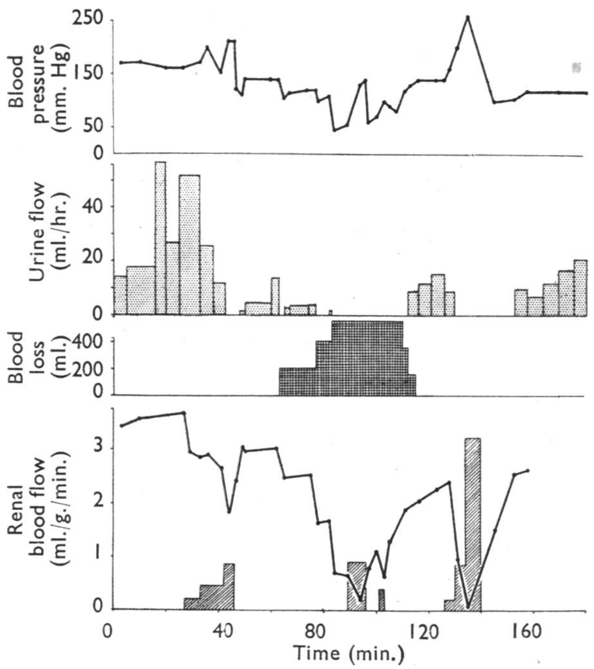

FIG. 7.—Dog, 18 kg., chloralosane 120 mg./kg. Showing the effect of acute haemorrhage on the blood flow and urine formation in transplanted kidneys, and the effects of noradrenaline (bottom section, striped rectangles; × 10 μg./kg./min.) before, during, and after the blood loss.

again. Further infusions of noradrenaline in varying doses showed that 2 μg./kg./min. had no definite effect on urine flow or renal blood flow, whereas 8.7 μg./kg./min. reduced renal blood flow to 1.0 ml./g./min. and stopped the flow of urine, and 32.3 μg./kg./min. reduced renal blood flow to 0.07 ml./g./min. On stopping the noradrenaline, the renal blood flow returned to 2.6 ml./g./min. after 13 min. and urine flow restarted.

DISCUSSION

The effects of noradrenaline on renal function have usually been studied by clearance techniques. These can only be used in the presence of a free urine flow, and they are more suited to experiments in which conditions remain constant, rather than to those in which marked variations in blood pressure, renal blood flow, and urine flow occur.

My experiments, in which the kidneys of one dog were transplanted into the neck of another dog, have permitted repeated direct measurements of renal blood flow irrespective of the urine flow. They have confirmed previous reports of reduction in renal blood flow with noradrenaline (man: Barnett, Blacket, Depoorter, Sanderson, and Wilson, 1950; Werkö, Bucht, Josephson, and Ek, 1951; King and Baldwin, 1956; dog: Pickford and Watt, 1951; Moyer and Handley, 1952). They have shown that the blood flow may be completely arrested; this arrest occurred abruptly on starting the noradrenaline infusion, and recovered rapidly on stopping the drug.

Urine flow decreased progressively with increasing doses of noradrenaline, and anuria was repeatedly observed. The blood pressure during the anuric periods was often only moderately raised and was rarely at those levels found in patients with a phaeochromocytoma. The extent to which renal blood flow falls during the hypertensive crises in such patients is not known, but albuminuria is commonly found (Howard and Barker, 1937; Fertig, Taylor, Corcoran, and Page, 1951), and anuria, oliguria, and azotaemia may occur (Labbé, Tinnel, and Doumer, 1922; MacKeith, 1944).

Moyer, Handley, and Huggins (1954), in studying the renal response to noradrenaline in dogs made hypotensive by repeated haemorrhage, reported that the restoration of normal blood pressure was accompanied by improvement in renal function provided the haemorrhage was not severe, but that, if severe, noradrenaline might cause a further reduction in the renal blood flow. Moyer, Morris, and Beazley (1955) studied the renal changes in man during severe haemorrhagic shock and after normal tension had been restored by noradrenaline. They found that noradrenaline might improve the renal function, but that complete restoration required an increase in the blood volume. In my experiments, hypotension induced by haemorrhage was accompanied by marked oliguria or anuria and by a considerable fall in the renal blood flow. On restoring the blood pressure to normal with noradrenaline, anuria persisted and the renal blood flow fell still further or, as in one dog, stopped completely. A rapid restoration of urine and renal blood flow followed the reinjection of blood.

Whereas all but one of the present studies on urine flow were performed on innervated kidneys *in situ*, the blood flow measurements were carried out on transplanted, and therefore denervated, kidneys. Denervation of the kidneys in dogs has been reported to increase the sensitivity to noradrenaline (Berne, Hoffman, Kagan, and Levy, 1952). In the one experiment in which I studied the urine flow of the transplanted kidneys the dose of noradrenaline causing anuria was comparable with that having a similar effect in the innervated kidneys. This supports the observation of Pickford and Watt (1951) that denervation did not alter the sensitivity of the kidneys of the dog to noradrenaline.

SUMMARY

1. In anaesthetized dogs urine flow was progressively reduced by increasing doses of (±)-noradrenaline. When anuria occurred, with sufficiently high dose, the systolic blood pressure was 200 mm. Hg or less in most dogs.

2. Noradrenaline produced an abrupt fall in, and sometimes complete arrest of, renal blood flow.

3. Reduction in urine and renal blood flow followed acute haemorrhage. Further reduction occurred when the blood pressure was restored with noradrenaline. Renal function rapidly recovered on reinjection of the removed blood.

4. Similar renal changes may possibly occur in patients during the crises from a phaeochromocytoma, or receiving noradrenaline in post-haemorrhagic shock.

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