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Water Diuresis from Clonidine (Catapres) (38979)

STRAVROS G. CHRYSANTHAKOPOULOS AND A. R. LAVENDER

(Introduced by R. D. Lindeman)

Divisions of Renal and Hypertension, Hines V. A. and Loyola University Hospitals at Hines, Maywood, Illinois 60153

Available clinical and experimental evidence indicates that clonidine 2-2(2,6-dichlorophenylamino)-2 imidazoline hydrochloride, has potent hypotensive, bradycardic and bradypneic properties (1–6). It also produces sedation and local anesthesia, inhibits gastric acid secretion, and raises blood sugar (7). Its effect on blood pressure in the anesthetized dog is a bimodal one. An initial short rise is followed by a prolonged decrease. Similar observations have been reported in the rabbit, rat, and cat (8, 9). Concerning the actions of clonidine upon renal hemodynamic and excretory functions, it was shown by Onesti *et al.* (6) that when the drug was given either orally or intravenously to dogs and man, it had no effect on the effective renal plasma flow, glomerular filtration rate, and potassium excretion, while it decreased the excretion of sodium and chloride. The pathophysiologic mechanism by which clonidine exerts its renal effects has not as yet been elucidated. The purpose of this study, therefore, was to attempt to clarify if clonidine has any direct renal effect by infusing the drug in small amounts into the renal artery of one kidney of the anesthetized dog and comparing its effects against the other kidney without disturbing systemic hemodynamics. In a second group of animals the drug was given intravenously in order to study the systemic effects and significance of a different route of administration.

Materials and methods. Sixteen well-conditioned dogs of both sexes weighing 22–25 kg were used in this study. The animals were anesthetized with sodium pentobarbital (30 mg/kg) and kept lightly anesthetized for the whole length of the experiments. All the animals were intubated and ventilated with room air. The jugular vein and the external carotid artery were exposed and catheterized with polyethylene tubing for continuous infusion and monitoring of the blood pressure, respectively. The dogs were primed with a solution containing inulin and para-aminohippuric acid (PAH) in isosmotic saline. Thereafter the dogs were maintained with a sustaining solution of similar composition but different concentration administered at a rate of 6.0 ml/min, in order to maintain the dog's blood levels of inulin and PAH at 25–30 mg% and 2–4 mg%, respectively.

A mercury manometer was connected to the external carotid artery for continuous monitoring of the blood pressure and blood sampling from a manifold. Both ureters were exposed through a midline incision and catheterized with polyethylene tubing for continuous urine collection into graduated cylinders. In 10 dogs (Group 1) the right renal artery was exposed through a left flank incision and cannulated through the abdominal aorta with an 18-gauge Rochester needle for infusion of the drug. In six dogs (Group 2) the drug was given intravenously. The experiments in both groups were divided into a control and experimental period. The control period consisted of four urine collections 20 min each and the experimental period of six collections 20 min each also. Blood for clearances of inulin and PAH was drawn between urine collections. During the control period, the right renal artery in Group 1 dogs and the external jugular vein in Group 2 were each infused with isosmotic saline 1.2 ml/min. During the experimental period, the right renal artery and external jugular vein were infused with isosmotic saline containing 1.2 μg and 12.0 μg of clonidine per minute, respectively. Urine and blood samples were analyzed for Na, K, Cl, Ca, PO_4, and osmolality. The urine volume total and differential for the two kidneys and the excretion of sodium ($U_{Na}V$), potassium (U_KV),

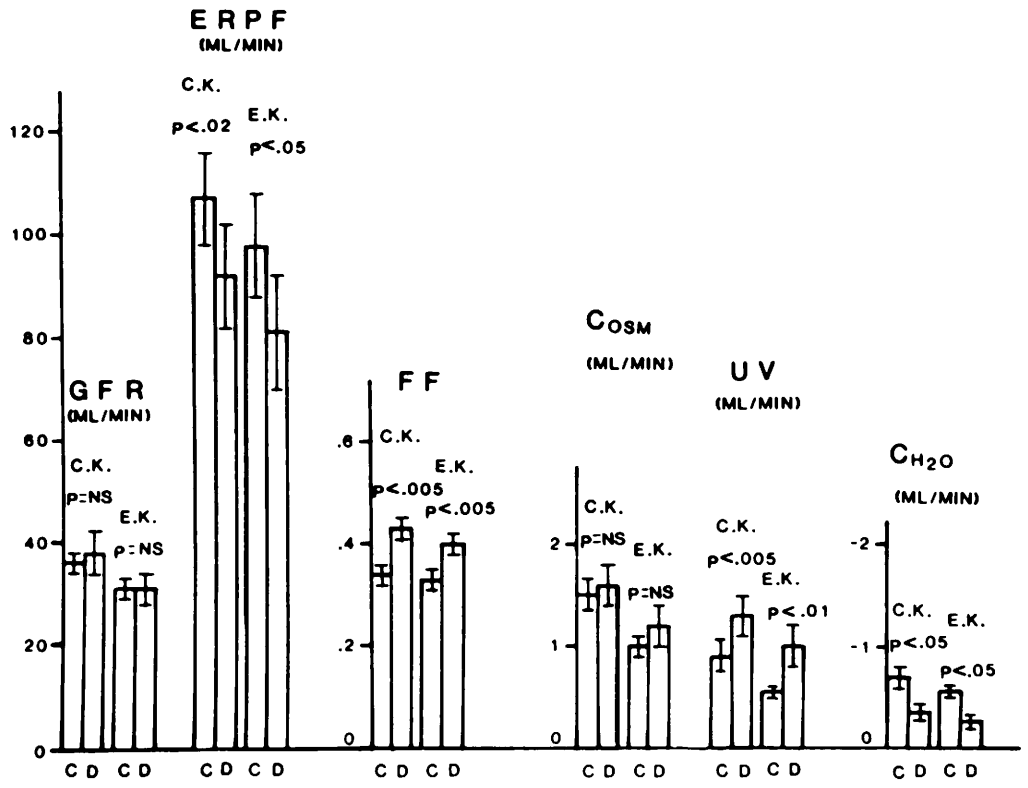

FIG. 1. This figure shows the mean values for the control kidney (C.K.) and experimental kidney (E.K.) for glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (FF), osmolar clearance (Cosm), urine volume (UV), and free water clearance (C_{H_2O}) during control (C) and drug administration (D). The *P* values show the significance of the differences in values before and after the drug administration for each kidney in Group 1 animals.

chloride ($U_{Cl}V$), calcium ($U_{Ca}V$), phosphorous ($U_{PO_4}V$), osmolar and free water clearance were also determined. Vital signs included blood pressure (BP), heart rate (HR), and respiratory rate (RR). After the last urine collection in Group 1 dogs, malachite green was infused into the right renal artery and the kidney was inspected for uniform distribution of the dye. The dogs in whom the right kidney was not uniformly stained were excluded from the study. The findings from each kidney were averaged for each period and the mean value of the control period for each individual kidney was substracted from the experimental period. The mean differences then were tested for significance by Students' *t* test. In Group 2 dogs the same procedure was followed and the mean differences of both kidneys for the two periods were also statistically tested by Students' *t* test. A *t* test was also applied for the changes in vital signs for the two groups of animals.

Results. Group 1 Dogs. A. *Renal hemodynamic alterations.* The GFR was not significantly affected in neither kidney by clonidine; however, the ERPF was decreased in both kidneys ($P < .05$, $P < .02$) and the filtration fraction increased ($P < .005$, $P < .005$), also bilaterally (Fig. 1).

B. *Renal excretory changes.* The renal excretion of sodium, chloride, potassium, calcium, phosphorous and also the osmolar clearance were not significantly affected by clonidine in either kidney. However, the free water clearance and urine volume were increased significantly by clonidine from both kidneys, e.g., the TCH_2O decreased with clonidine (Figs. 1 and 2).

Group 2 Dogs. A. *Renal hemodynamic al-*

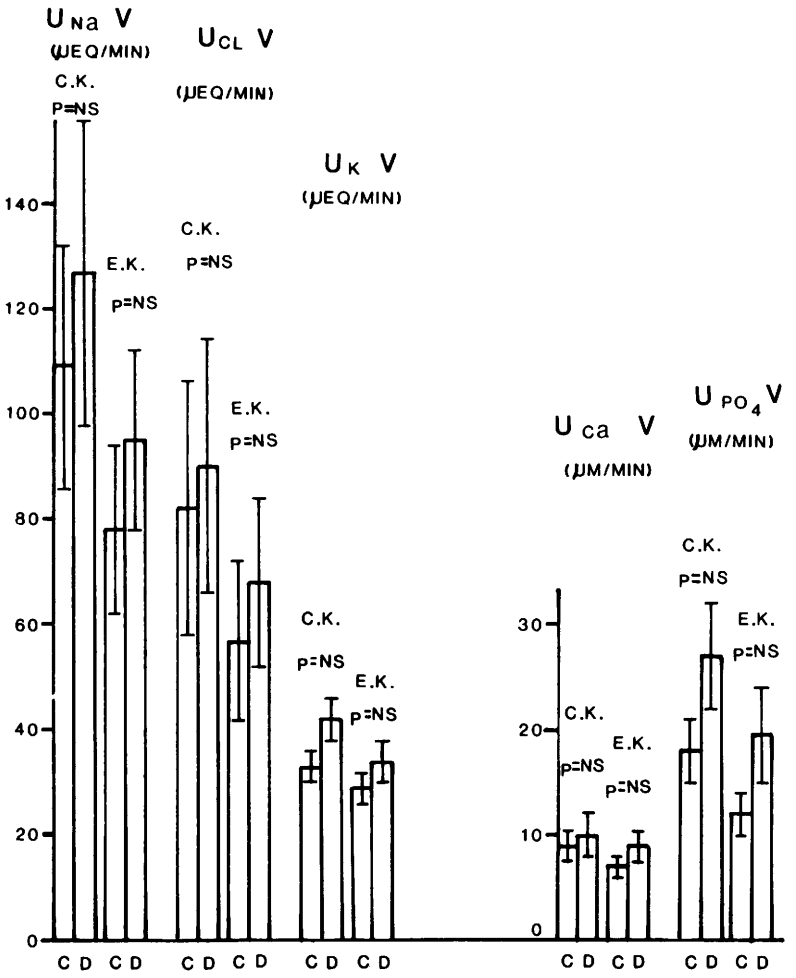

FIG. 2. This figure depicts the mean values for the excretion of sodium ($U_{Na}V$), chloride ($U_{Cl}V$), potassium (U_KV), calcium ($U_{Ca}V$), and phosphorus ($U_{PO_4}V$) for the control (CK) and experimental kidneys (EK), during control (C) and drug administration (D). The p values show the significance of the differences for each kidney before and after drug administration in Group 1 animals.

terations. The ERPF was significantly decreased ($P < .02$) while the filtration fraction was significantly increased by clonidine ($P < .05$) (Fig. 3).

B. *Renal excretory changes*. The renal excretion of sodium and chloride were decreased by clonidine ($P < .02$, $P < .05$), while the excretion of potassium, calcium, phosphorous, and osmolar clearance were not significantly affected. On the other hand the free water clearance and urine volume were increased by clonidine ($P < .005$, $P < .02$) (Figs. 3 and 4).

Systemic effects. The mean arterial systolic pressure was significantly increased in Group 1 animals ($P < .005$) while it was not affected in Group 2 animals. On the other hand, the heart and respiratory rates were significantly decreased in both groups of animals ($P < .001$, $P < .005$; $P < .001$, $P < .001$) (Figs. 5 and 6). Clonidine, regardless of the route of administration induced light sedation in both groups of animals so that they did not require any additional pentobarbital during the time clonidine was being administered. On the other hand, during the control periods in both groups of animals, pentobarbital in

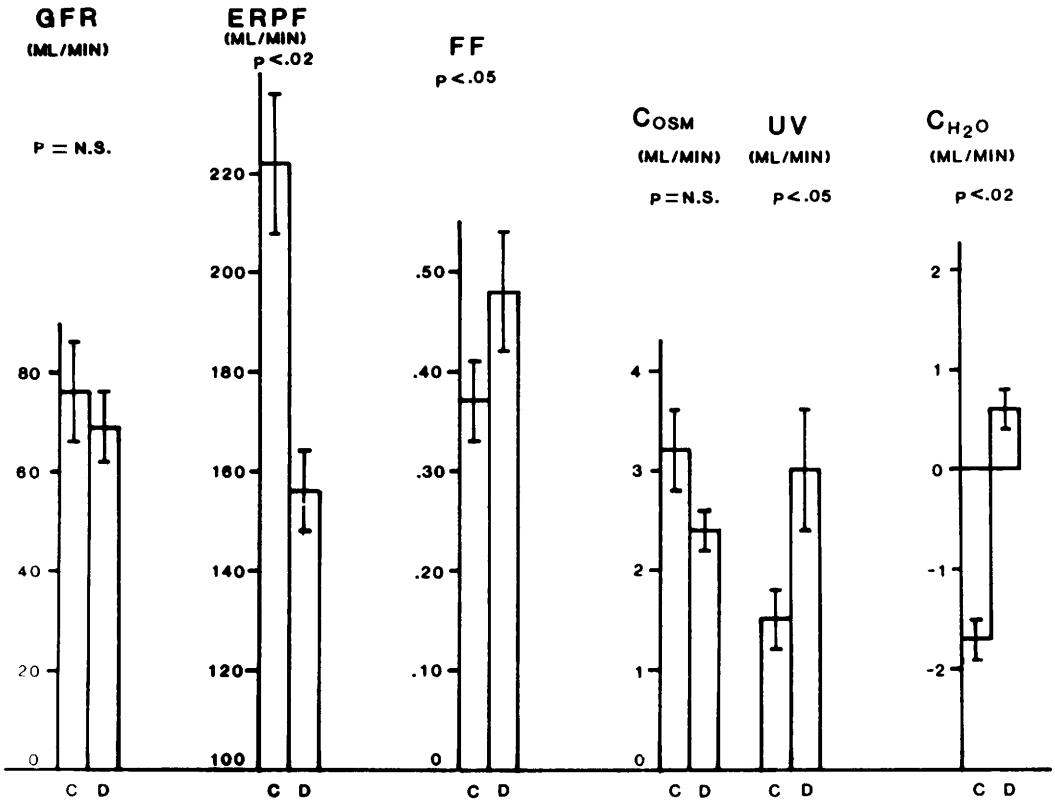

FIG. 3. This figure shows the mean values for GFR, ERPF, FF, Cosm, UV, and C_{H_2O} for both kidneys before and after drug administration in Group 2 animals.

small doses had to be given hourly in order to keep the animals lightly anesthetized.

Discussion. Our studies suggest that clonidine given in small amounts directly into the renal artery of the anesthetized dog produces severe arteriolar constriction probably affecting both afferent and efferent arterioles, as the GFR is not altered, the ERPF is decreased, and consequently the filtration fraction is increased (Figs. 1 and 3). These changes are similar to those produced by sympathomimetic amines and several investigators have suggested that clonidine has properties similar to those of the potent sympathomimetic amines epinephrine and norepinephrine (5–8, 10, 11). Others have stated that clonidine exerts its effects by directly stimulating the alpha-adrenergic receptors since most of its effects can be prevented or blocked by phenoxybenzamine, an alpha-adrenergic receptor blocking agent (8, 10, 12–14). Specifically, Boissier *et al.* (8) have shown that in anesthetized animals, the hypertension, the contraction of the nictitating membrane of cats and isolated seminal vesicles of guinea pigs, and the vasoconstriction of isolated rabbit ears induced by clonidine in normal as well as reserpinized and adrenalectomized animals could be suppressed or abolished by phentolamine. The effects of clonidine upon the excretory functions of the kidney are striking. Clonidine uniformly increased the urine volume and free water clearance in both groups of animals without affecting osmolar clearance. In small amounts it had no effect upon electrolyte excretion (Fig. 2), while in larger amounts it significantly decreased the excretion of sodium and chloride (Fig. 4). Similar observations have been previously reported by Onesti *et al.* (6). However, in our studies, the ERPF was decreased while in those reported by Onesti, there was no change in ERPF. The discrepancy could

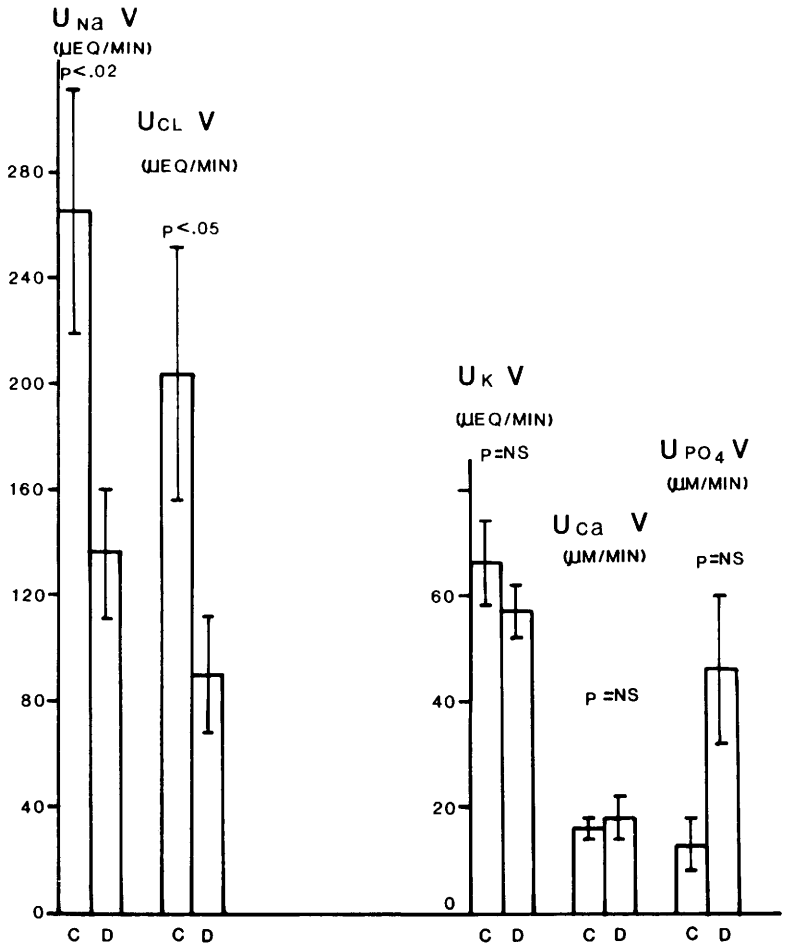

FIG. 4. In this figure are shown the mean values for $U_{Na}V$, $U_{Cl}V$, U_KV, $U_{Ca}V$, and $U_{PO_4}V$ for both kidneys before and after the administration of clonidine in Group 2 animals.

be dose-related since clonidine has been shown to possess a dual effect upon the alpha-adrenergic receptors. In small amounts it acts as an alpha-adrenergic receptor agonist (15), while in larger doses as an antagonist (8, 12). These properties of clonidine could explain its different effect upon the blood pressure in the two groups of animals. In small amounts it increased BP (Fig. 5), while in larger amounts it had no effect upon the BP (Fig. 6). However, this is not the only mechanism by which clonidine affects BP. Its main hypotensive effect is being mediated through central inhibition of sympathetic outflow (2, 4, 10, 14, 16–18). The sodium and chloride retaining effects of clonidine could be explained on the basis of increased oncotic pressure of the peritubular capillaries as has previously been described (19–24) or to redistribution of blood flow from the outer salt wasting cortical nephrons into deeper corticomedullary salt retaining nephrons. Similar changes have been described with hemorrhage or stimulation of the renal nerves (25, 26). Renal vasodilation leads to opposite effects (27). The enhanced sodium reabsorption by the ascending limb of Henle's loop could account for the increased free water clearance seen in our experiments. However, the increase in urine flow cannot be explained on this basis and one has to postulate a central antidiuretic hormonal inhibitory effect of clonidine. Indeed, Berl *et al.* (27) have

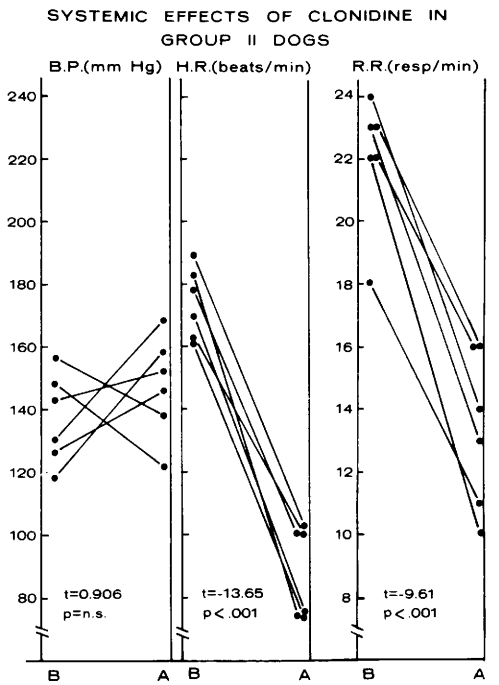

FIG. 5. In this figure the effects of clonidine upon blood pressure (BP), heart rate (HR), and respiratory rate (RR) during intrarenal infusion (1.2 μg/min) of the drug are shown. In small amounts clonidine exerted a pressor effect upon the BP, while its effects upon HR and RR were depressant.

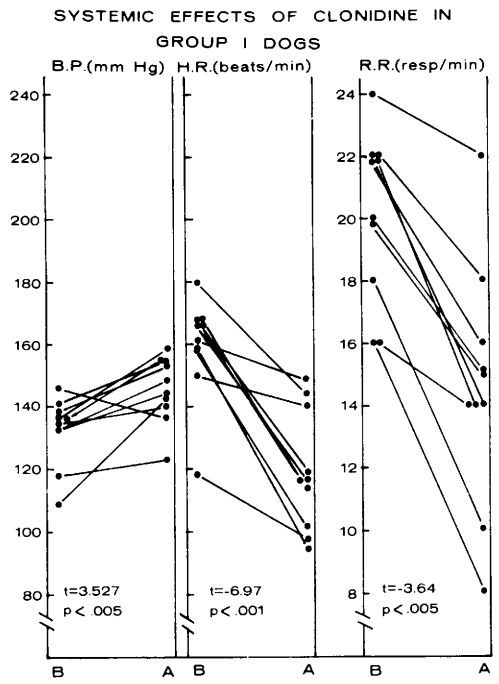

FIG. 6. This figure depicts the effects of clonidine upon BP, HR, and RR during intravenous administration (12.0 μg/min), of the drug. In larger amounts clonidine lost its pressor properties, while its depressant effects upon HR and RR were accentuated.

shown that alpha-adrenergic agonists suppress ADH release centrally while beta-adrenergics have a stimulatory effect on ADH release. Therefore, clonidine being an alpha-adrenergic receptor agonist, could well suppress ADH release and explain the increase in free water clearance. A local tubular anti-ADH effect of clonidine is not likely since alpha-adrenergic receptor agonists have no effect in patients with nephrogenic diabetes insipidus (28). Whatever its cause, these effects are striking and have not been reported previously. Therefore, they deserve further study. The bradycardic and bradypneic actions of clonidine are mediated through, possibly, a central effect upon the cardiorespiratory center. The latter effect could explain the prolonged periods of sinus arrest seen in our animals.

Summary. The renal hemodynamic and excretory effects of clonidine were tested in two groups of dogs. In one group, the drug was given directly into the renal artery at a rate of 1.2 μg/min and resulted in a significant decrease of the effective renal plasma flow (ERPF) in both kidneys, an increase in filtration fraction (FF), urine volume (UV), and free water clearance (C_{H_2O}) and had no effect upon the glomerular filtration rate (GFR), osmolar clearance (Cosm) and the excretion of sodium ($U_{Na}V$), chloride ($U_{Cl}V$), potassium (U_KV), calcium ($U_{Ca}V$) and phosphorous ($U_{PO_4}V$). No unilateral effect was appreciated. In the second group of animals it was given intravenously at a rate of 12.0 μg/min and resulted in a significant decrease of ERPF, $U_{Na}V$, $U_{Cl}V$, and increase in FF, UV, and C_{H_2O}) but had no effect upon GFR, Cosm U_KV, $U_{Ca}V$ and $U_{PO_4}V$. Systemically, it decreased heart rate (H.R.) and respiratory rate (R.R.) in both groups of animals; it increased blood pressure (BP) in Group 1 and had no effect on BP in Group 2.

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