Effect of Chlorothiazide on Renal Blood Flow in the Conscious Dog[1] (35018)

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Previous studies dealing with the effect of thiazides on renal hemodynamics have indicated that these agents increase renal vascular resistance and decrease renal blood flow. Hook *et al.* (1) administered hydrochlorothiazide (3 mg/kg, intravenously) to dogs in which one kidney was autoperfused at a constant rate. They reported an increase in renal vascular resistance following administration of hydrochlorothiazide. Cassin and Vogh (2), using an electromagnetic flow meter in dogs to assess hemodynamic changes, observed that 5 mg/kg of hydrochlorothiazide (a maximally effective natriuretic dose) given intravenously had no effect on renal blood flow, but that higher doses (10 mg/kg, intravenously, and 30 mg/kg, intravenously) produced a significant reduction in renal blood flow. In a study by Asperia (3) chlorothiazide was given intravenously in a priming dose of 15 mg/kg and infused at the rate of 15 mg/kg/hr. Using a dye dilution method, an increase in renal vascular resistance and a decrease in renal blood flow were found. In the studies cited above, the animals were anesthetized with sodium pentobarbital. Inasmuch as renal vascular resistance is elevated in animals anesthetized with pentobarbital (4, 5) it is possible that the action of the thiazides could have been affected. In this report, unanesthetized dogs were used to assess the effect of chlorothiazide on renal hemodynamics.

Methods. Chronic animals were prepared in the following manner. Female mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg, iv). The left renal artery was approached retroperitoneally through a flank incision. An electromagnetic flow transducer (Carolina Medical Electronics; lumen size, 11-mm circumference, or *In Vivo* Metric Systems, lumen size, 3.5-mm diam) was placed around the exposed renal artery. The transducer cable was passed through the flank muscle layers and subcutaneously to the neck region just superior to the scapulae. Here the cable was externalized with a subcutaneous connector extruding through the skin. Another small incision was made just medial to the right forelimb over the region where the omocervical artery branches from the subclavian artery in order to expose the omocervical artery. A cannula (Silastic Medical-Grade Tubing, 0.040-in. id., 0.085-in. od., Dow Corning Corp.) to be used to monitor blood pressure was inserted into the exposed omocervical artery such that the tip of the cannula was located in the subclavian artery. The cannula was passed subcutaneously to the dorsal neck region (same area in which the flow transducer was externalized) and externalized with a nylon connector (6) extruding through the skin. The animals were given an intramuscular injection of 400,000 units of penicillin and 0.5 g of streptomycin daily for 3 days following surgery and were allowed at least 2–3 days to recover from the surgery before experimentation.

During an experiment the dogs were placed in a sling such that their feet just touched the floor. This allowed the animals to either stand in place or hang in the sling as they so desired. The externalized flow transducer cable and cannula were attached to an electromagnetic flow meter (Carolina Medical Electronics, Model 321) and pressure transducer, respectively. Both renal blood flow and systemic blood pressure were recorded continuously on a Beckman oscillo-

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graph. Renal vascular resistance was determined by dividing mean arterial blood pressure (mm Hg) by renal blood flow (ml/kg/min) and is expressed as units of resistance. A Foley bladder catheter was inserted to collect urinary samples. Urinary collection periods were 20 min in length. The bladder was given three 30-ml air rinses spaced by two 15 ml water rinses between collection periods. A single 20-min urinary collection period preceded and three 20-min urinary collection periods followed intravenous administration of chlorothiazide (5 mg/kg).

The data were analyzed statistically using the Student's one-tail *t* test, paired comparisons (7). The 0.05 level of probability was used as the criterion of significance.

Results and Discussion. When 5 mg/kg of chlorothiazide was administered to unanesthetized dogs, an almost immediate decrease in renal blood flow was observed. Blood pressure was not altered markedly. A composite of the blood flow tracings from 3 animals (Fig. 1) shows the characteristics of the chlorothiazide-induced decrease in renal blood flow. The maximal drug-induced decrease in renal blood flow occurred within 5 min after administration. Renal blood flow was still decreased significantly at 10 and 20 min after drug administration but had returned to the control level of flow by 30 min after administration of chlorothiazide. The effects of chlorothiazide on sodium excretion as well as hemodynamics are shown in Table I. The values for sodium excretion are expressed on a per kilogram of total body weight basis. Chlorothiazide increased sodium significantly in all urinary collection periods and the increase was about the same in all periods. It should be noted that sodium excretion was increased significantly during the period of reduced renal blood flow and increased renal vascular resistance and remained elevated after renal blood flow and resistance had returned to the control levels. Blood pressure was not altered by this dose of the drug.

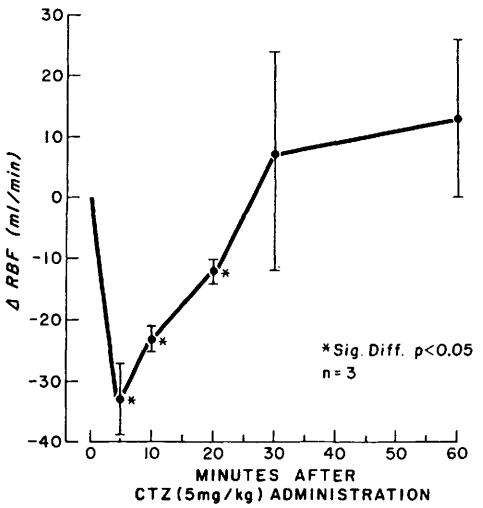

FIG. 1. Effect of chlorothiazide (CTZ) (5 mg/kg) on renal blood flow in unanesthetized dogs. The tracing shows the change in renal blood flow after drug administration. Vertical lines indicate standard errors. Renal blood flow prior to CTZ administration was 237 ± 19 ml/min.

TABLE I. Effect of Chlorothiazide (CTZ) on Sodium Excretion and Renal Hemodynamics in the Conscious Dog.[a]

		After CTZ (min)				
	Control	5	10	20	30	60
RBF (ml/kg/min)	13.8	11.8[b] (±0.1)	12.4[b] (±0.1)	13.1[b] (±0.1)	14.2 (±1.0)	14.6 (±0.8)
R (units)	6.2	7.1[b] (±0.2)	6.8[b] (±0.2)	6.7[b] (±0.1)	6.3 (±0.2)	5.8 (±0.2)
BP (mm Hg)	87	84 (±1)	85 (±3)	88 (±1)	88 (±1)	85 (±4)

		After CTZ (min)		
		0–20	20–40	40–60
$U_{Na}V$ (μeq/kg/min)	2	22[b] (±2)	24[b] (±4)	22[b] (±3)

[a] Values indicate means. Values in parentheses indicate standard error of the difference from control.
[b] Denotes significant difference from control.

Renal blood flow was decreased by 5 mg/kg of chlorothiazide in the present study in which conscious animals were employed while 5 mg/kg of hydrochlorothiazide appeared to have no effect on renal blood flow in anesthetized dogs (2). These data suggest that conscious animals may be more susceptible to the renal vasoconstricting action of the thiazides than anesthetized animals.

In the study of Asperia (3) it was reported that the chlorothiazide induced increase in sodium excretion was correlated with the increase in renal vascular resistance induced by this agent. This correlation was interpreted as indicating that sodium transport was involved in controlling renal vascular tone. In these experiments, chlorothiazide was infused continuously. While data were reported which showed that the increase in renal vascular resistance and the increase in sodium excretion occurred at similar times and that both changes were maintained while chlorothiazide was infused, no information was given regarding the relationship of these actions after stopping the infusion of chlorothiazide. The data in the experiments reported here show that the thiazide-induced change in renal vascular resistance lasts less than 30 min after a single injection of chlorothiazide whereas the action of the drug on sodium excretion persists for a much longer period. Thus the previously reported correlation would not appear to be valid.

Summary and Conclusions. The effect of chlorothiazide on renal blood flow was assessed in conscious dogs in which flow transducers and pressure cannulas were chronically implanted. The results show that chlorothiazide (5 mg/kg, intravenously) increased renal vascular resistance and consequently decreased renal blood flow. It appears that a small drug-induced increase in renal vascular resistance can produce a rather substantial decrease in renal blood flow. It also appears that conscious animals may be more susceptible to the renal vasoconstricting action of the thiazides than anesthetized animals. The drug-induced decrease in renal blood flow lasted less than 30 min whereas the drug-induced increase in sodium excretion was still near maximal at 60 min.

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