THE EFFECT OF CHLOROTHIAZIDE ON SEPARATE KIDNEY FUNCTION IN ESSENTIAL HYPERTENSION

BY

HERMAN VILLARREAL, FRANCISCO LARRONDO, JOSÉ EMILIO EXAIRE,
AND ANDRÉS REVOLLO

From the Nephrology Department, National Institute of Cardiology, Mexico

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Recently, it has been shown that significant differences in hæmodynamic behaviour and electrolyte excretion exist between one kidney and the other early in the course of essential hypertension (Baldwin *et al.*, 1960). The possibility has been considered that these differences are indicative of an intrinsic renal disturbance that could be responsible for the hypertensive process.

The purpose of this study was to investigate whether or not these differences could be modified by a drug, such as chlorothiazide, which, besides its antihypertensive action, has a direct effect upon renal function.

MATERIAL AND METHODS

Ten patients with essential hypertension were studied: 7 were at an early stage, as judged by the relatively minor renal functional impairment, and 3 had moderate kidney damage. In addition to the clinical diagnosis of essential hypertension, intravenous urograms were made and no evidence of disparity in renal size or function was found. Subsequently, the index proposed by Rapoport (1960) was calculated and gave values from 0.76 to 1.49.

All patients were at rest, on low salt diet, normal fluid intake, and placebo. Blood pressure was taken under basal conditions and when stabilized, i.e. within 6 to 13 days, the study was begun.

The patients were catheterized to 15 cm. above the ureteral meatus using 7F and 8F catheters in order to collect urine from each kidney. Another catheter was placed in the bladder to detect leakage around the ureteral catheters. Those patients in whom urine was found in the bladder were excluded from this study.

Fifteen minutes after catheterization the renal function studies were begun. After injection of priming doses of inulin and p-aminohippurate, a sustaining infusion of these substances dissolved in 5 per cent glucose was administered at a constant rate of 1 ml. per minute by means of a Bowman pump.

Urine and blood samples were taken during two periods totalling 60 minutes for determination of glomerular filtration rate (C_{in}), renal plasma flow (C_{PAH}), and water and sodium excretion.

In all 500 mg. chlorothiazide was administered intravenously, and urine and repeat blood samples were collected during two periods in 60 minutes.

Inulin was determined by a modification of Harrison's method (Goldring and Chasis, 1944), and p-aminohippurate by the method of Smith *et al.* (1945). Sodium was determined in a Baird flame photometer.

In the control period, as well as after the administration of chlorothiazide, readings of the arterial blood pressure were taken every five minutes. The average of these was used to calculate the mean arterial blood pressure which was considered as the sum of diastolic pressure plus one-third of pulse pressure.

The percentage differences between the two kidneys were calculated by dividing the difference between them by their mean value.

TABLE I
HÆMODYNAMIC BEHAVIOUR OF THE SEPARATE KIDNEYS BEFORE AND AFTER INTRAVENOUS ADMINISTRATION OF
CHLOROTHIAZIDE IN 10 PATIENTS WITH ESSENTIAL HYPERTENSION

Patient	Sex and age (yr.)	Mean arterial blood pressure (mm. Hg)		Glomerular filtration rate (ml./min.)						Renal plasma flow (ml./min.)					
		Control	Chlorothiazide	Control			Chlorothiazide			Control			Chlorothiazide		
				Right	Left	% diff.	Right	Left	% diff.	Right	Left	% diff.	Right	Left	% diff.
L. B.	F 35	120	103	63	65	3	56	63	12	176	164	7	149	196	27
S. M.	F 49	137	106	55	63	13	41	53	25	185	204	10	181	215	17
C. G.	M 37	130	107	54	57	5	43	50	15	250	250	0	330	319	3
A. G.	F 49	130	107	64	64	0	52	53	0	175	166	5	178	169	5
S. P.	F 22	130	107	65	60	8	61	57	7	269	259	4	277	269	3
J. C.	M 28	127	112	74	54	31	30	34	12	326	228	35	184	187	0
I. S.	M 40	128	113	53	62	16	42	45	8	164	183	11	160	169	6
V. G.	M 26	157	140	22	34	43	19	27	35	80	103	25	85	120	34
M. A.	M 27	173	140	33	28	16	31	32	3	101	104	3	99	98	0
A. V.	M 42	163	157	18	18	0	19	20	5	54	50	8	51	57	10

$$\text{Per cent difference} = \frac{\text{Difference}}{\frac{1}{2}(\text{right kidney} + \text{left kidney})} \times 100,$$

and the result was considered significant only when greater than 15 per cent (Hulet *et al.*, 1960).

RESULTS

Table I shows mean arterial blood pressure and renal hæmodynamic values as well as the percentage difference between the two kidneys. Urinary volume, concentration, and excretion of sodium (V , U_{Na} , and $U_{Na}V$) and their percentage differences appear in Table II.

Under the action of chlorothiazide, mean arterial blood pressure dropped in the 10 patients studied, reaching normal values in five.

Glomerular filtration rate was found to be different in 4 patients during the control period. Under the action of chlorothiazide, differences disappeared in 3 patients (J. C., I. S., M. A.) and persisted in 1 (V. G.). In S. M. in whom glomerular filtration rate was the same in both kidneys, a significant difference appeared after administration of the drug.

Two patients were found with difference in renal plasma flow during the control period.

TABLE II
SODIUM EXCRETION OF THE SEPARATE KIDNEYS BEFORE AND AFTER INTRAVENOUS ADMINISTRATION OF
CHLOROTHIAZIDE IN 10 PATIENTS WITH ESSENTIAL HYPERTENSION

Patient	Urinary volume (ml./min.)						Urinary concentration of sodium (mEq/l.)						Urinary excretion of sodium (μ Eq/min.)					
	Control			Chlorothiazide			Control			Chlorothiazide			Control			Chlorothiazide		
	Right	Left	% diff.	Right	Left	% diff.	Right	Left	% diff.	Right	Left	% diff.	Right	Left	% diff.	Right	Left	% diff.
L. B.	0.21	0.28	28	1.15	1.30	12	90	93	3	156	173	10	19	26	31	179	225	23
S. M.	0.78	0.82	5	1.02	1.47	36	43	63	38	161	171	6	34	52	42	164	252	42
C. G.	0.20	0.20	0	1.36	1.42	4	104	163	44	189	285	40	21	33	44	252	405	45
A. G.	0.31	0.30	3	1.03	1.19	14	121	122	0	155	182	16	38	37	2	160	217	30
S. P.	2.79	2.50	11	2.90	2.60	11	9	8	12	76	73	4	25	19	27	222	190	15
J. C.	1.28	0.30	124	1.03	0.93	10	10	36	112	126	121	4	13	11	18	130	113	14
I. S.	0.50	0.55	9	1.84	1.89	3	180	203	12	183	217	17	90	112	22	337	411	20
V. G.	0.50	0.97	64	2.47	4.32	54	88	92	10	87	88	0	44	89	68	216	379	54
M. A.	0.88	0.99	12	1.95	2.00	3	44	30	38	145	110	27	39	30	26	284	221	25
A. V.	0.32	0.32	0	2.06	2.47	18	59	50	16	91	93	0	19	16	17	188	229	19

Under the action of chlorothiazide, the discrepancies persisted in 1 patient (V. G.) and disappeared in the other (J. C.). In 2 (L. B., S. M.), in whom no differences were found, disparities appeared after administration of the drug.

Urinary volume was different in 3 patients before the administration of chlorothiazide. In 1 of them (V. G.), discrepancy persisted during its effect, while in the other 2 (L. B., J. C.) it disappeared. In 2 patients (S. M., A. V.) in whom urine volume was the same in both kidneys during the control period, significant differences appeared under the action of the drug.

Disparities in urinary sodium concentration were observed in 5 patients during the control period. These persisted in 2 of them (C. G., M. A.) and disappeared in 3 (S. M., J. C., A. V.) when chlorothiazide was administered. In two patients (A. G., I. S.) discrepancies appeared under the action of the drug.

Differences in sodium excretion were present in 9 patients before chlorothiazide was given and in 8 after.

DISCUSSION

According to Hulet *et al.* (1960), the most satisfactory method for studying differences between one kidney and the other is the non-parametric percentile method. This permits comparison of two positive values, the difference between which increases until one of them reaches zero. The parametric method, on the other hand, may yield negative values and lead to error since the frequency curve of the variation of the phenomenon does not always follow a normal distribution.

Hulet, applying the non-parametric percentile method to normal subjects arbitrarily classed differences between the two kidneys below the ninetieth percentile group as normal. The differences in this group gave an upper limit of 15 per cent, i.e. only inequalities greater than 15 per cent can be considered significant.

During the control period, differences in accordance with the above criterion were observed in one or more of the functions studied in 9 out of our 10 patients (Tables I and II). These data confirm the findings of Baldwin *et al.* (1960).

As was expected (Villarreal *et al.*, 1962) glomerular filtration rate decreased under the action of chlorothiazide, but reductions were of different magnitude in each kidney as a result of which discrepancies disappeared or appeared. Differences persisted only in one patient.

Patients with the highest blood pressure readings during the control period did not always show differences in glomerular filtration rate, nor did the extent of these discrepancies bear any relation to the blood pressure levels. Similarly, no correlation was found between level of blood pressure and differences in glomerular filtration rate as a result of the action of chlorothiazide.

Although this drug does not significantly modify renal plasma flow (Villarreal *et al.*, 1962), it did affect this function unequally in the two kidneys in such a way that differences disappeared or appeared. Only in one instance did the difference encountered in the control period persist during the action of chlorothiazide. As in the case of glomerular filtration rate, discrepancies in renal plasma flow bore no relation to arterial blood pressure variations.

The greatest number of disparities between one kidney and the other was found in sodium excretion both before and after administration of chlorothiazide (Fig. 1 and 2). These disparities were due to differences in urinary sodium concentration in some patients and in urinary volume in others. In 3 patients (L. B., S. P. and I. S.), however, the differences could not be attributed to either of these two factors. These results seem to suggest that the statistical method used has limitations when applied to derived data, such as $U_{Na}V$, since insignificant differences in each factor when varying in the same direction may become significant when multiplied.

Although in our patients the incidence of differences in sodium excretion in the control period is comparable to that indicated by Baldwin, the causes are not the same, since in his cases they were the result of discrepancies in water excretion while in ours they were mainly due to inequalities of urinary sodium concentration. The greater incidence of disparities in urinary sodium concentration in the present study may be related to its low value in some patients.

FIG. 1.—Incidence of significant differences between one kidney and the other before administration of chlorothiazide in 10 patients with essential hypertension. (G.F.R., glomerular filtration rate; R.P.F., renal plasma flow; V, urinary volume; UNa, urinary concentration of sodium; UNaV, urinary excretion of sodium.)

FIG. 2.—Incidence of significant differences between one kidney and the other during the acute effect of chlorothiazide in 10 patients with essential hypertension. (Key as for Fig. 1.)

The number of patients with differences in sodium excretion was greater than that with disparities in glomerular filtration rate and hence in sodium load. This indicates that the discrepancies in sodium excretion were due mainly to a tubular disorder.

Study of the effect of chlorothiazide upon the functional differences between one kidney and the other in essential hypertension indicates that under the action of this drug these discrepancies may disappear or appear, except for sodium excretion which tends to persist, in spite of the fact that the range of sodium excretion is different before and during the effect of the substance.

The persistence of differences in sodium excretion indicates its importance in essential hypertension. However, it does not establish whether these differences are related to the genesis of this process or are a consequence of it.

SUMMARY

Differences in the haemodynamic behaviour and electrolyte excretion between one kidney and the other have been found early in the course of essential hypertension. The purpose of this study was to investigate whether chlorothiazide, a drug having antihypertensive action and a direct effect on renal function, would modify these differences.

Ten patients with essential hypertension were catheterized in order to study the function of each kidney before and after the intravenous administration of chlorothiazide. During the control period, differences were observed in 9 out of the 10 patients in one or more of the functions studied. Under the action of chlorothiazide, blood pressure dropped in all patients, while discrepancies in renal haemodynamics and water and sodium excretion persisted in some instances and disappeared or appeared in others.

The greatest number of discrepancies between the kidneys was found in sodium excretion, both before and after administration of chlorothiazide, and were attributable to functional tubular disturbances.

It is concluded that (1) functional differences between the kidneys in essential hypertension have no relation to arterial blood pressure levels; (2) under the action of chlorothiazide disparities between the kidneys may disappear or appear, indicating that they are functional in nature; (3) difference in sodium excretion between one kidney and the other is one of the most frequent

discrepancies in essential hypertension. This difference may be attributed to a tubular functional inequality that persists during the action of chlorothiazide.

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