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## Effect of diuretic therapy on ventricular arrhythmias in hypertensive patients with or without left ventricular hypertrophy

Recent studies have suggested that hypertensive patients with ECG evidence of left ventricular hypertrophy (LVH) may have increased risk of sudden death when treated with diuretics. In the present study echocardiography was used as a more sensitive index for the presence of LVH. Thirty-one patients with uncomplicated hypertension underwent 48-hour ambulatory ECG monitoring both before any treatment and after 4 weeks of hydrochlorothiazide (HCTZ), 100 mg daily. In 18 patients with left ventricular posterior wall thickness (LVPWT)  $\geq 13$  mm (average =  $14.4 \pm 0.2$  mm) on echocardiogram, plasma potassium decreased from  $4.1 \pm 0.3$  to  $3.3 \pm 0.4$  mEq/L with HCTZ ( $p < 0.01$ ). Premature ventricular contractions (PVCs) averaged  $5.7 \pm 9.9$ /hr at baseline and  $7.1 \pm 16.6$ /hr following HCTZ ( $p = \text{NS}$ ). The total number of couplets was 29 before and 13 after HCTZ, while four brief runs of ventricular tachycardia occurred only before treatment. In the remaining 13 patients with LVPWT  $\leq 12$  mm (average =  $11.2 \pm 0.1$  mm), plasma potassium decreased from  $4.1 \pm 0.3$  to  $3.4 \pm 0.5$  mEq/L with HCTZ ( $p < 0.01$ ). The average number of PVCs was  $4.3 \pm 8.0$ /hr before and  $5.2 \pm 8.9$ /hr after HCTZ ( $p = \text{NS}$ ). One couplet and one 3-beat run of ventricular tachycardia occurred before and one 3-beat run of ventricular tachycardia after HCTZ. Although more complex arrhythmias were noted in the LVH group, the differences were not statistically significant. These results indicate that thiazide therapy does not increase ventricular arrhythmias either in patients with or without LVH. (AM HEART J 110:595, 1985).

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Diuretics have been used in the management of systemic hypertension for more than 20 years and have been considered to be safe and effective. Certain known side effects of diuretics, however, have recently become a matter of concern. While the biochemical consequences of diuretic administration, such as hyperuricemia, hyperglycemia, or increase in cholesterol, are cause for more concern, hypokalemia remains the major issue. Fear that mild to moderate hypokalemia may aggravate cardiac arrhythmias has resulted in the massive administration of potassium supplements and potassium-sparing diuretics<sup>1</sup> and, more recently, has caused a shift away from the use of diuretics in the treatment of hypertension. This trend has gained popularity

even though an association between hypokalemia and cardiac arrhythmias not only remains unproved but is seriously challenged.<sup>1,2</sup> Nevertheless, recently published studies have been widely interpreted as establishing an association between diuretic therapy and cardiac arrhythmias<sup>3</sup> or sudden death.<sup>4</sup> In the latter publication,<sup>4</sup> a subgroup of thiazide-treated hypertensive patients with baseline ECG abnormalities was identified as high risk for sudden death. The ECG abnormalities included evidence of left ventricular hypertrophy (LVH), nonspecific ST-T wave changes, and minor conduction defects. Although an association between hypokalemia and increased risk of sudden death could not be demonstrated, diuretic therapy was suggested as the possible cause and has been widely accepted by most physicians.

The present study was designed to investigate the effects of diuretic therapy on cardiac arrhythmias in patients with essential hypertension in the presence or absence of LVH.

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**Table 1.** Patient characteristics at baseline

Characteristics	Patients with LVH (n = 18)	Patients without LVH (n = 13)
Age (yr)	57 ± 10	50 ± 9
Blood pressure (mm Hg)		
Systolic	154 ± 16	150 ± 7
Diastolic	100 ± 9	97 ± 19
Body weight (kg)	84 ± 15	92 ± 19
Plasma potassium (mEq/L)	4.1 ± 0.3	4.1 ± 0.3
Plasma sodium (mEq/L)	143 ± 6	142 ± 5
Plasma chloride (mEq/L)	107 ± 6	106 ± 6
Plasma bicarbonate (mEq/L)	26 ± 4	24 ± 4
Plasma glucose (mg/dl)	105 ± 12	101 ± 13
Plasma creatinine (mg/dl)	1.2 ± 0.3	1.1 ± 0.2
LVPWT by echocardiography (mm)	14.4 ± 0.12	11.2 ± 0.08*
No. of patients with LVH by ECG	13	1*

LVPWT = left ventricular posterior wall thickness; LVH = left ventricular hypertrophy.

Estes scoring system was used to assess the presence of LVH by ECG.

\* $p < 0.01$ ; all other values were not statistically different.

## METHODS

**Patients.** Thirty-four patients with essential systemic hypertension entered the study. Most of the patients were known to develop hypokalemia during treatment with thiazide diuretics. All patients were black men. Patients with a history of myocardial infarction, angina pectoris, congestive heart failure, renal insufficiency (creatinine  $\geq 2.0$  mg/dl), inability to give informed consent, or those who required digitalis therapy were excluded from the study. Three patients were terminated from the trial because of noncompliance and failure to attend clinic visits.

**Screening phase.** Following the history and physical examination a chest roentgenogram, echocardiogram, ECG, complete blood count, and blood chemistries were obtained from all patients. Patients with evidence of heart disease other than LVH were excluded from the study. The presence or absence of LVH was determined from the echocardiogram by measuring the left ventricular posterior wall thickness (LVPWT) prior to the mechanical contraction of the left atrium.<sup>5</sup> Measurement of LVPWT was considered adequate evidence of LVH, since patients with asymmetric septal hypertrophy or dilated heart disease (left ventricular diastolic dimension  $> 52$  mm) were excluded from the study. Patients with LVPWT  $\geq 13$  mm comprised the group of patients with LVH, whereas the remaining patients comprised the group without LVH. The presence or absence of LVH was also determined by ECG criteria by means of the Estes scoring system.<sup>6</sup>

**Study protocol: Phase 1-baseline.** After eligibility for the study was determined all medications were discontinued and potassium chloride, 40 mEq daily, was given to all patients for 10 days. Three weeks later patients were seen for baseline studies. Sitting blood pressure, heart rate,

body weight, and plasma creatinine, sodium, potassium, and chloride were determined. Blood samples were collected in sterilized 10 ml tubes that contained 143 units of lithium heparin and were analyzed within 30 minutes. Within 30 minutes after blood samples were obtained a 48-hour ambulatory ECG monitoring was initiated. Immediately after completion of the 48-hour recording, a second blood sample for electrolyte determinations was obtained. The average plasma potassium of these two measurements comprised the plasma potassium of this phase.

**Phase 2—hydrochlorothiazide (HCTZ) therapy.** Following the completion of phase 1, all patients were started on HCTZ, 50 mg twice daily, which continued for 4 weeks. At the end of this period and while HCTZ therapy continued all studies described in phase 1, including 48-hour ECG monitoring, were repeated.

**Ambulatory ECG monitoring.** Ambulatory ECG monitoring was carried out for 48 hours during each phase by means of a double-channel model 425 Avionics recorder, and analysis was performed on a Cardiodata MK<sub>3</sub> 2 channel cardioscanner. Analysis of all tapes was carried out by an experienced technician. For quality control, 10% of the tapes were analyzed by a second technician. Less than 10% interobserver variability was found. In addition, samples from each hour of recording, including the important arrhythmias, were printed on hard copy in real time and were reviewed by one of the authors.

Ventricular arrhythmias were tabulated in two ways: (1) by means of a modification of the Lown classification as used by Singh et al.,<sup>7</sup> that is: 0 = no premature ventricular contractions (PVCs); 1 = PVCs 1 to 29/hr; 2 = PVCs  $\geq 30$ /hr; 3 = multiform PVCs; 4 = couplets; 5 = ventricular tachycardia. From this grading system an average grade/hour was calculated. (2) Average number of PVCs/hour, total number of couplets, and total number of ventricular tachycardia episodes.

Statistical analysis of the results was performed where appropriate by means of Student's *t* test for paired observations or chi-square test. The study was approved by the Research and Development Committee at the VA Medical Center, Washington, DC.

## RESULTS

Of the 31 patients who completed the study, 18 were found to have LVH on echocardiogram, whereas the remaining 13 did not meet the criteria for LVH. As shown in Table I the only statistically significant difference between the two groups was the presence or absence of LVH. LVPWT averaged  $14.4 \pm 0.12$  mm in the first group and  $11.2 \pm 0.88$  mm (mean  $\pm$  SD) in the second group ( $p < 0.01$ ). In the first group 13 of the 18 patients met the ECG criteria for LVH, while only one patient in the second group had criteria of probable LVH. All other characteristics including age, blood pressure, body weight, and blood chemistries were similar in the two groups.

**Table II.** Patients with LVH (n = 18)

	Before HCTZ	After HCTZ
Plasma potassium (mEq/L)	4.1 ± 0.3	3.3 ± 0.4*
Average PVCs/hr	5.7 ± 9.9	7.1 ± 16.6
Total couplets	29	13
Total episodes of ventricular tachycardia	4	0
Average grade/hr	0.77 ± 0.77	0.78 ± 0.83

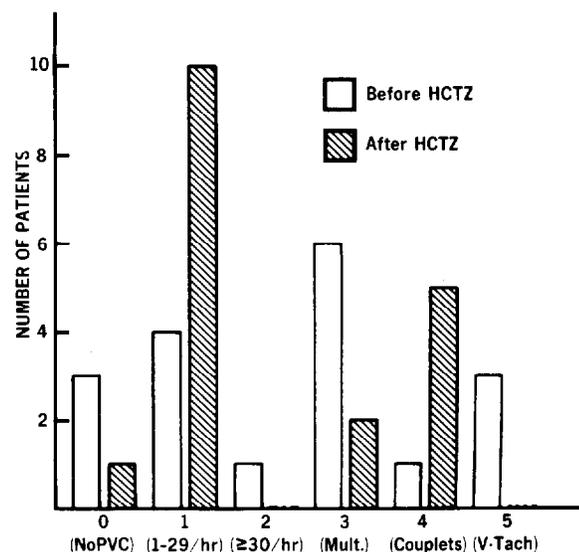
HCTZ = hydrochlorothiazide; PVCs = premature ventricular contractions.

\**p* < 0.01.

**Arrhythmias before and after hydrochlorothiazide**

*Patients with LVH.* In the group of patients with LVH the baseline plasma potassium prior to HCTZ therapy was 4.1 ± 0.3 mEq/L and decreased to 3.3 ± 0.4 mEq/L (*p* < 0.01) with HCTZ (Table II). The average number of PVCs/hour was 5.7 ± 9.9 at baseline and 7.1 ± 16.6 after HCTZ (*p* = NS). The total number of couplets in all patients was 29 before and 13 after HCTZ, whereas four brief (three to four beats) episodes of ventricular tachycardia occurred only at baseline. The average grade/hour, which is an index of frequency, complexity, and probably severity of the arrhythmias, did not change with HCTZ therapy. Tabulation of these 18 patients according to their highest grade of arrhythmia is shown in Fig. 1. At baseline three patients had brief runs of ventricular tachycardia, one patient had couplets, six patients had multiform PVCs, and one patient had PVCs ≥30/hr. Following HCTZ no patient had runs of ventricular tachycardia, five patients had couplets, and two patients had multiform PVCs. Overall 11 patients had ≥ grade 2 arrhythmias at baseline and seven following HCTZ.

*Patients without LVH.* The 13 patients in this group had an average plasma potassium of 4.1 ± 0.3 mEq/L at baseline, which decreased to 3.4 ± 0.5 mEq/L following HCTZ (*p* < 0.01) (Table III). The average number of PVCs/hour was 4.3 ± 8.0 before and 5.2 ± 8.9 after HCTZ (*p* = NS). One brief episode of ventricular tachycardia was noted before and one couplet and one episode of ventricular tachycardia after HCTZ. The average grade/hour did not change with HCTZ. Tabulation of these patients according to their highest grade of arrhythmia is shown on Fig. 2. At baseline one patient had a brief run of ventricular tachycardia, two patients had multiform PVCs, and one patient had PVCs ≥30/hr. Following HCTZ one patient had a brief run of ventricular tachycardia, one had one couplet, and two had multiform PVCs. Arrhythmias greater than



**Fig. 1.** Patients with LVH (n = 18). Patients were tabulated according to their highest grade of arrhythmia. A modification of the Lown classification was used.<sup>7</sup>

grade 2 were present in four patients before and in four after HCTZ.

When the two groups of patients are compared it appears that patients with LVH tended to have more frequent PVCs and higher grade arrhythmias than the patients without LVH. However, the differences were not statistically significant.

With reference to the variability in ventricular ectopy between the two consecutive 24-hour ambulatory ECG monitorings during each phase, it is noteworthy that up to a fourfold difference in the frequency of PVCs was noted in the same patient during the same phase on consecutive 24-hour recordings. More important, couplets or runs of ventricular tachycardia were noted on one but not the other 24-hour monitoring during the same phase.

**DISCUSSION**

The objective of this study was to determine whether patients with LVH are prone to malignant ventricular arrhythmias when treated with HCTZ as compared to patients without LVH. Echocardiographic rather than ECG criteria were used for definitions of LVH because of the known higher sensitivity of the former technique.<sup>8</sup> Indeed, in this study of the 18 patients shown by echocardiography to have LVH only 13 had definite or probable evidence of LVH on ECG. For the purpose of the study patients with essential hypertension but free of any other chronic disease were selected. Patients were divided at entry into two groups, those with

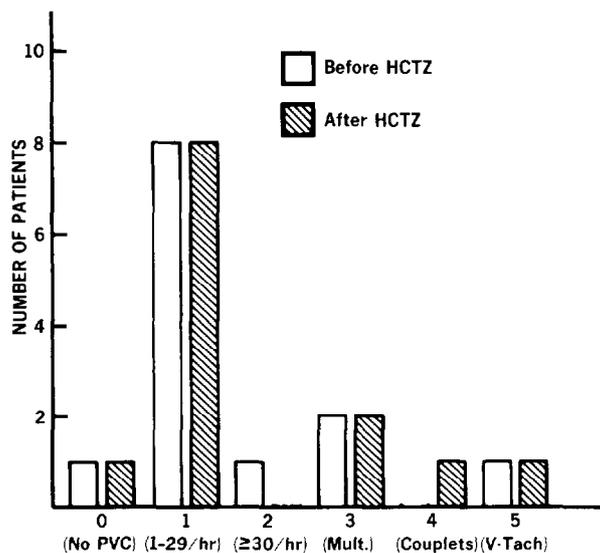


Fig. 2. Patients without LVH ( $n = 13$ ). Patients were tabulated according to their highest grade of arrhythmia.

and those without LVH. Patients in the two groups were similar in every other respect.

**Diuretic therapy.** Results in this study provided no evidence that HCTZ therapy causes an increase in cardiac arrhythmias. In fact, in the group of patients with LVH there was a slight but statistically insignificant decrease in the more complex arrhythmias. Although the group of patients with LVH had a slightly higher number of PVCs/hour and more complex arrhythmias than the group of patients without LVH, the differences were not statistically significant. Both groups had a similar decrease in plasma potassium following HCTZ therapy.

**Multiple Risk Factor Intervention Trial.** These results are contrary to the current belief that diuretic therapy and diuretic-induced hypokalemia may increase cardiac arrhythmias and the incidence of sudden death, especially in hypertensive patients with baseline ECG abnormalities. This impression has mainly been derived from the recently published data of the Multiple Risk Factor Intervention Trial.<sup>4</sup> That study failed to show a decrease in the mortality rate in the more aggressively treated special intervention group as compared to the usual care group. Further analysis of the data showed an increased mortality rate in a subgroup of patients with ECG abnormalities at entry (mostly high R waves compatible with LVH). Although the authors of the study<sup>4</sup> cautioned that their findings were inconclusive and further investigation was needed, these data have frequently been used to establish an association between thiazide therapy and increased

Table III. Patients without LVH ( $n = 13$ )

	Before HCTZ	After HCTZ
Plasma potassium (mEq/L)	$4.1 \pm 0.3$	$3.4 \pm 0.5^*$
Average PVCs/hr	$4.3 \pm 8.0$	$5.2 \pm 8.9$
Total couplets	0	1
Total episodes of ventricular tachycardia	1	1
Average grade/hr	$0.45 \pm 0.50$	$0.49 \pm 0.62$

For abbreviations, see Table II.

\* $p < 0.01$ .

risk of sudden death in patients with baseline ECG abnormalities.<sup>9</sup> Furthermore, although no correlation was observed between serum potassium level and sudden death, hypokalemia was nevertheless blamed as a cause of the increased risk of malignant arrhythmias and sudden death.<sup>9</sup> Interestingly, the Hypertension Detection and Follow-Up Program<sup>10</sup> in a recent reanalysis of their data failed to confirm the Multiple Risk Factor Intervention Trial findings.

**Medical Research Council Trial.** Whether or not hypokalemia is a cause of cardiac arrhythmias is controversial. The Medical Research Council Trial of Great Britain<sup>3</sup> showed no increase in cardiac arrhythmias in a group of patients monitored before and after thiazide therapy for 8 to 10 weeks (short-term group). Increased ventricular ectopy was found in another group of patients treated with thiazide diuretics for an average of 2 years (long-term group) as compared to placebo-treated patients. In the latter group there was no significant association between the number of PVCs and serum potassium levels, although there was a significant correlation with uric acid concentration.

The authors of the previously mentioned study concluded that the changes in serum potassium and uric acid probably were acting as markers of thiazide intake and were not causally associated with cardiac arrhythmias. The results of the present study are in agreement with the results in the short-term group of the Medical Research Council trial. Others<sup>11</sup> have found an association between thiazide-induced hypokalemia and cardiac arrhythmias, but their results have been questioned.<sup>1,2</sup>

In this study patients with LVH tended to have more arrhythmias than patients without LVH, both at baseline and following diuretic therapy. However, the differences did not reach statistical significance. Previous studies<sup>12</sup> have indeed shown that the presence of LVH determined by ECG criteria predisposes to a higher incidence of arrhythmias.

Although the electrophysiologic changes associ-

ated with diuretic therapy are unknown, theoretically mild to moderate diuretic-induced hypokalemia in patients with uncomplicated systemic hypertension could be associated with more electrical stability and less cardiac arrhythmias. It has been shown by many investigators that diuretic therapy is mainly associated with a decrease of extracellular potassium but only minimal change in intracellular potassium concentration.<sup>13-16</sup> These changes result in hyperpolarization of the cell membrane,<sup>2,17,18</sup> which could lead to an increased threshold of excitation, increased rate of rise of phase 0, and improvement in conduction, which could eliminate reentrant circuits and thus improve electrical stability. With potassium levels much lower than those usually achieved by diuretics phase 3 may lengthen to the point that subsequent beats intercept hypopolarized cells and promote reentry.

**Conclusions.** The data presented in this study do not support an association between thiazide therapy and increased ventricular arrhythmias in patients either with or without LVH.

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