

Hypertension and Sudden Death

Disparate Effects of Calcium Entry Blocker and Diuretic Therapy on Cardiac Dysrhythmias

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• This study was designed to evaluate the impact of antihypertensive therapy on cardiac dysrhythmias in 13 hypertensive patients who received calcium entry blockers and in 10 hypertensive patients who received hydrochlorothiazide. Mean arterial pressure fell to a similar extent in both treatment groups; however, left ventricular mass index decreased (from 102 ± 4 to 95 ± 2 g/m²) only in patients receiving calcium entry blockers, but not in those taking hydrochlorothiazide. The prevalence of premature ventricular contractions decreased 74% from 21 ± 14 /h to 5.7 ± 6 /h in the calcium entry blocker group, but did not change in the hydrochlorothiazide group (15 ± 17 /h to 16 ± 13 /h). Couplets, multiform contractions, ventricular tachycardia, and supraventricular tachycardia were completely abolished after calcium entry blocker therapy, whereas the prevalence of these arrhythmias remained unchanged during treatment with hydrochlorothiazide. We conclude that antihypertensive therapy with calcium entry blockers (but not with thiazide diuretics) reduces left ventricular mass and the prevalence and severity of ventricular dysrhythmias. Whether this reduction will improve the ominous prognosis of left ventricular hypertrophy and diminish the risk of sudden death remains unknown.

(Arch Intern Med. 1989;149:1263-1267)

Calcium entry blockers have been proven to be effective and safe agents in the treatment of coronary artery disease¹⁻⁵ and essential hypertension.⁶⁻⁷ Calcium entry blockers not only reduce arterial pressure levels by decreasing total peripheral resistance, but may also be useful in allowing left ventricular hypertrophy (LVH) to regress.⁸⁻¹³ Moreover, calcium entry blockers have emerged as a new class of antiarrhythmic agents,¹⁴ their most striking action being a prompt termination of most supraventricular arrhythmias and some forms of ventricular ones.¹⁴⁻²¹

For many years, thiazide diuretics have been used as first-line agents in the stepped-care approach of antihypertensive

therapy.^{22,23} They are still used extensively because they are inexpensive, effective, and well tolerated. However, concern has been expressed that long-term thiazide diuretic therapy may predispose to cardiac dysrhythmias.²⁴⁻²⁸ Also, some recent studies have shown that despite a reduction in arterial pressure, LVH does not diminish when thiazide diuretics are given.²⁹⁻³⁰

This study was designed to evaluate cardiac dysrhythmias before and after effective antihypertensive therapy with calcium entry blockers and with diuretics in a selected group of hypertensive patients who had ambulatory electrocardiographic documentation of ventricular ectopy.

PATIENTS AND METHODS

The study population consisted of 23 patients with essential hypertension. Established essential hypertension was said to be present if diastolic pressures measured in the outpatient clinic were consistently higher than 90 mm Hg. All patients had appropriate clinical and laboratory evaluation to exclude secondary forms of hypertension. We also excluded patients with overt coronary artery disease or other organic heart diseases as evidenced by clinical, electrocardiographic, and echocardiographic criteria. Exercise treadmill testing was done in some patients when clinically indicated.

In all patients who had been previously treated, antihypertensive medication was discontinued at least 4 weeks before entry in the study. Patients qualified for the study if they had any ventricular dysrhythmias during 24-hour Holter monitoring and if their diastolic pressure was equal to or greater than 90 mm Hg and less than 115 mm Hg on at least two consecutive outpatient visits.

Ambulatory electrocardiographic monitoring (Del Mar Avionics) was performed during a 24-hour period starting and ending at 9 AM. Each tape was initially scanned at high speed (Dynamic Electrocardioscanner, model 655, Del Mar Avionics), and subsequently reviewed for detailed analysis by two independent investigators who were unaware of other study results at the time of the analysis. A printout was obtained of the complete 24-hour recording. Left ventricular function and structure were assessed by M-mode echocardiography (guided by two-dimensional echo). Measurements were obtained following the recommendations of the American Society of Echocardiography.³¹ Left ventricular mass was calculated according to the formula of Troy et al³² and corrected by body surface area. Also, a 12-lead electrocardiogram was recorded in all patients and blood was drawn to measure serum electrolyte levels.

The therapeutic goal was to achieve diastolic pressure values equal

Accepted for publication February 10, 1989.

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Table 1.—Arterial Pressure and Left Ventricular Function Before and After Therapy With Calcium Entry Blockers and Hydrochlorothiazide

	Calcium Entry Blockers		Hydrochlorothiazide	
	Before	After	Before	After
Systolic pressure, mm Hg	165 ± 6	132 ± 4*	152 ± 16	137 ± 14*
Diastolic pressure, mm Hg	90 ± 2	81 ± 3*	98 ± 14	86 ± 9.2*
Mean arterial pressure, mm Hg	116 ± 2	98 ± 3*	115 ± 10	103 ± 9.0*
Heart rate, bpm†	76 ± 8	72 ± 9	64 ± 5.0	63 ± 12
Ejection fraction, %	73 ± 2	76 ± 3	65 ± 3.0	67 ± 10
Fractional fiber shortening, %	37 ± 4	38 ± 2	36 ± 3.0	38 ± 7.0

**P* < .001 (before and after antihypertensive therapy).

†bpm indicates beats per minute.

Table 2.—Left Ventricular Structure Before and After Therapy With Calcium Entry Blockers and Hydrochlorothiazide

	Calcium Entry Blocker		Hydrochlorothiazide	
	Before	After	Before	After
Septal wall thickness, cm	1.20 ± 0.9	1.18 ± 0.7	1.33 ± 0.34	1.30 ± 0.38
Posterior wall thickness, cm	1.10 ± 0.8	1.0 ± 0.3*	1.12 ± 0.21	1.10 ± 0.16
Relative wall thickness	45 ± 1.2	42 ± 1.1*	42 ± 6.8	42 ± 8.4
Left ventricular mass, g	200 ± 7.0	175 ± 4.0*	290 ± 115†	290 ± 118†
Left ventricular mass index, g/m ²	102 ± 4.0	95 ± 2.0*	146 ± 58	146 ± 60

**P* < .05 (before and after antihypertensive therapy).

†*P* < .05 (calcium entry blocker group vs hydrochlorothiazide group).

Table 3.—Prevalence of Cardiac Arrhythmias Before and After Therapy With Calcium Entry Blockers and Hydrochlorothiazide*

	Calcium Entry Blockers, No. (%)		Hydrochlorothiazide, No. (%)	
	Before	After	Before	After
Simple PVCs	13/13 (100)	5/13 (26)	10/10 (100)	10/10 (100)
Coupled PVCs	7/13 (85)	0/13 (0)	7/10 (70)	9/10 (90)
Multiform PVCs	5/13 (26)	0/13 (0)	8/10 (80)	10/10 (100)
Ventricular tachycardia	4/13 (25)	0/13 (0)	4/10 (40)	3/10 (30)
Supraventricular tachycardia	4/13 (25)	0/13 (0)	5/10 (50)	5/10 (50)

*PVCs indicate premature ventricular contractions.

to or lower than 90 mm Hg. At the beginning of the active treatment phase patients were seen weekly, and the dose of the antihypertensive agent was titrated to achieve an optimal response. Once diastolic pressure was below 90 mm Hg, patients were followed up every 2 weeks. After the 8- to 12-week period of treatment each patient underwent another complete physical examination, 24-hour Holter monitoring, echocardiogram, and 12-lead electrocardiogram.

Calcium Entry Blocker Group

The calcium entry blocker group consisted of 13 men (12 white and 1 black), mean age, 48 ± 5 years, and mean body surface area, 1.86 ± 0.7 m². Seven patients had echocardiographic evidence of LVH,³⁸ and only three patients had electrocardiographic evidence of LVH. All patients received calcium entry blockers for an 8-week period. Five patients were given verapamil in the sustained release formulation (range, 120 to 480 mg/d); four patients, diltiazem (range, 60 to 480 mg/d); and four patients, isradipine (range, 5 to 15 mg/d).

Hydrochlorothiazide Group

The hydrochlorothiazide group consisted of 10 hypertensive patients: 5 men and 5 women; 6 white and 4 black; mean age, 50 ± 8 years; and mean body surface area, 1.90 ± 0.1 m². Eight patients had echocardiographic evidence of LVH, and six patients had electrocardiographic evidence of LVH.³⁸ All patients received hydrochlorothiazide in doses ranging from 50 to 100 mg/d.

Statistical Methods

Analysis of variance with repeated measurements was used to compare values before and after treatment. Statistical significance of

prevalence of ectopic beats as well as complex ventricular arrhythmias was evaluated by χ^2 analysis.³⁴

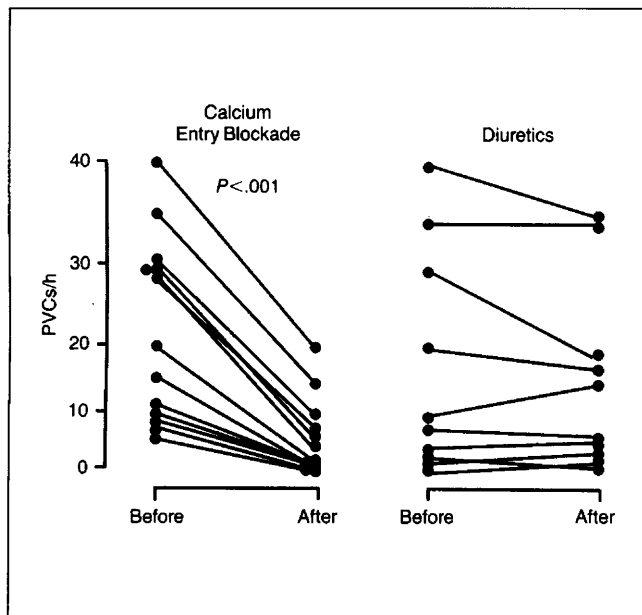
CLINICAL FINDINGS

Systolic, diastolic, and mean arterial pressures were significantly reduced by 10%, 12%, and 10%, respectively, after treatment with calcium entry blockers and 11% change with hydrochlorothiazide (Table 1), whereas heart rate, ejection fraction, and fractional fiber shortening did not change in either group (Table 1).

In the calcium entry blocker group, septal and posterior wall thickness decreased; consequently, left ventricular mass diminished by 13% and relative wall thickness by 7% (Table 2). In contrast, septal and posterior wall thickness, relative wall thickness, and left ventricular mass did not change after therapy with hydrochlorothiazide (Table 2).

Electrocardiographic time intervals P-R, QRS, QTc, and ST, and serum electrolyte levels remained unchanged after treatment in both groups. Serum potassium levels were 4.45 ± 0.4 mmol/L before and 4.20 ± 0.4 mmol/L after treatment in the hydrochlorothiazide group, and 4.09 ± 0.6 mmol/L before and 4.33 ± 0.5 mmol/L after treatment in the calcium entry blocker group. Potassium supplements were given when the serum potassium level fell below 3.5 mmol/L. Three patients received potassium supplements at the time of the second 24-hour Holter monitoring.

Prevalence and severity of ventricular ectopy were similar



Prevalence of premature ventricular contractions before and after antihypertensive therapy with calcium entry blockade and diuretics, respectively.

in the two groups before treatment (Table 3). The prevalence of premature ventricular contractions decreased 74% from $21 \pm 14/h$ to $5.7 \pm 6/h$ ($P < .001$) in the calcium entry blocker group, but did not change in the hydrochlorothiazide group ($15 \pm 17/h$ to $16 \pm 13/h$). Simple premature ventricular contractions were reduced by 74%, whereas couplets, multiform premature ventricular contractions, and ventricular and supraventricular tachycardias were completely suppressed with calcium entry blocker treatment (Table 3; Figure). Accordingly, patients treated with calcium entry blockers scored significantly lower with regard to the Lown's classification when compared with pretreatment grades. In contrast, neither the prevalence of simple premature ventricular contractions nor more complex cardiac dysrhythmias changed after hydrochlorothiazide treatment. Accordingly, average Lown's classification of the patients remained unchanged after hydrochlorothiazide treatment.

COMMENT

Cardiac adaptation to a prolonged increase in arterial pressure results in LVH. However, LVH is not merely a physiologic adaptive process serving to compensate for the increased afterload in essential hypertension.³⁵ Data from the Framingham cohort and later studies have clearly documented that LVH is an important risk factor for the development of subsequent cardiovascular morbidity and mortality.³⁶⁻³⁸ Our group has shown that patients with concentric LVH by electrocardiographic criteria have a higher prevalence of premature ventricular contractions and more complex ventricular arrhythmias than patients without LVH or normal subjects.³⁹ Similarly, hypertensive patients with eccentric LVH and isolated septal hypertrophy detected by echocardiographic criteria also have a higher prevalence of ventricular arrhythmias.^{40,41}

Our study indicates that short-term oral therapy with calcium entry blockers lowered arterial pressure, reduced left ventricular mass while preserving left ventricular function, and, most importantly, reduced the prevalence of ventricular ectopic beats and more complex arrhythmias. In

contrast, although hydrochlorothiazide lowered arterial pressure to the same extent and maintained left ventricular function similar to calcium entry blockers, it neither decreased left ventricular mass nor reduced ventricular ectopy. Both of these findings are in accord with previous clinical observations.^{22,23,29,30,42-45}

Calcium entry blockers (verapamil, diltiazem, and others) have a well-established therapeutic role in the acute termination of paroxysmal supraventricular tachycardia when given intravenously and, when administered orally, can prevent its recurrence.^{15-19,46-49} In contrast, the effect of calcium entry blockers on ventricular dysrhythmias is relatively ill defined.^{14,20,21} There is no datum showing that calcium entry blockers suppress ventricular ectopy in patients with chronic ischemic heart disease or in patients with normal hearts. Clinical experience suggests that calcium entry blockers have little or no effect in patients with chronic ventricular tachyarrhythmias or life-threatening ventricular arrhythmias^{38,50-52} (for a more comprehensive review, see reference 20). However, recent data indicate that the role of calcium entry blockers can suppress exercise-induced tachycardia in patients with coronary heart disease.⁵²⁻⁵⁴ Calcium entry blockers have also been effective in treating ventricular tachycardia occurring in young patients with otherwise normal hearts.⁵⁵⁻⁵⁸ Given this knowledge, the suppression of supraventricular tachycardia in our patients was no surprise. Unexpected, however, was the 74% reduction of ventricular ectopy and the complete suppression of ventricular couplets, multiform ventricular contractions, and more complex ventricular arrhythmias.

The exact mechanism by which LVH triggers cardiac arrhythmias is not completely understood. Anatomic factors such as enlarged myocytes, multiple intercalated disks, and small areas of fibrosis have been proven to facilitate intercellular current flow, and hence, intercellular conduction, producing areas of reentry mechanisms.⁵⁹⁻⁶¹ Mechanical factors such as the stretching of isolated myocardial cells have been shown to lower electric threshold amplitude and therefore increase automaticity.^{62,63} Furthermore, hypertensive patients with LVH are also at risk for subendocardial ischemia, since myocardial oxygen demand often exceeds oxygen supply, and coronary reserve is reduced.⁶⁴⁻⁶⁷

Four pathophysiologic mechanisms singly or in combination may account for the reduction of ventricular arrhythmias associated with calcium entry blockers in our study population. A decrease in LVH may reverse some of the above processes, at least as long as the left ventricle has not exceeded a certain critical mass. Coronary vasodilatation and the reduction in left ventricular mass may improve subendocardial ischemia^{9,64-69}; although none of our patients had clinical, electrocardiographic, or other evidence of myocardial ischemia, the possibility of microvascular disease⁷⁰ or latent ischemia cannot be ruled out. Calcium entry blockers may exert a direct antiarrhythmic effect on the electrically irritable myocardium.^{46,47,71} Diuretic-induced electrolyte imbalance may maintain or increase ventricular ectopy in diuretic-treated patients, and, conversely, the increase in potassium after calcium entry blockade may suppress ventricular ectopy. Finally, a fall in arterial pressure (reduction of the hemodynamic burden) also reduces left ventricular wall stress and stroke work, and therefore diminishes myocardial oxygen demands. Sideris et al⁷² found an acute elevation of arterial pressure with metaraminol therapy to induce premature ventricular contractions, whereas a reduction or disappearance of ventricular ectopy occurred after arterial pressure was lowered with nitroprusside therapy. However, the fact that diuretic therapy reduced arterial pressure to the same extent as therapy with calcium entry blockers, without improving

ventricular ectopy, argues against this latter mechanism (a reduction in arterial pressure) being the sole cause of the decrease in ventricular dysrhythmias in our study.

Clearly, the conclusive power of this study is limited since it was not done in a prospective double-blind randomized cross-over design. Also there were differences between the two treatment groups with regard to race, gender, and prevalence of LVH. Despite these potential drawbacks, our study suggests that antihypertensive therapy with calcium entry

blockers, but not with thiazide diuretics, reduces ventricular dysrhythmias. More studies involving larger numbers of patients and other antihypertensive drugs without intrinsic antiarrhythmic properties are needed to identify the exact electrophysiologic mechanism of this observation. Whether the decrease in left ventricular mass and suppression of ventricular ectopy associated with calcium entry blocker therapy will improve the ominous prognosis of LVH, and ultimately diminish the risk of sudden death, remains unknown.

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