

Circulatory Dose-response Effects of Hydrochlorothiazide at Rest and during Dynamic Exercise in Essential Hypertension

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A single oral daily dose of hydrochlorothiazide has been shown to provide effective 24-hour anti-hypertensive control of the resting blood pressure[1]. The modulation by thiazides of the pressor surges induced by daily activities in hypertensive patients has received little attention, although it has been suggested that hydrochlorothiazide may attenuate the rise in blood pressure during dynamic exercise[2]. The flat dose-response effect of thiazides on the blood pressure at rest has been described[3], but similar studies during dynamic exercise and with sustained therapy have not been undertaken.

The following investigation examined the influence of increasing doses of hydrochlorothiazide on the pressor responses to dynamic exercise in essential hypertension both at initiation of and during sustained anti-hypertensive therapy.

Methods

Patients

Twenty-four male patients aged 48 ± 2 (SEM) years (range 34 to 60) were studied; their mean supine pre-treatment blood pressure was $197 \pm 5/115 \pm 4$ mm Hg. All were asymptomatic and without evidence of target organ damage. Their average cardiothoracic ratio was 0.47 (range 0.41-0.52). Four patients had electrocardiographic left ventricular hypertrophy (Minnesota Code 3:1 or 3:3), 5 had incomplete right bundle branch block and 4 had minor T wave abnormality (Minnesota Code 5:2 or 5:3). Patients with a history of ischaemic heart disease, asthma, diabetes mellitus or peripheral vascular disease were specifically excluded from the study; no patient was taking concurrent anti-hypertensive or other medication. All subjects freely consented to participate in the study after being informed of its design and purpose. The study received the approval of the hospital ethics committee.

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Design of Investigation

The study investigated the immediate circulatory effects of 50 mg hydrochlorothiazide ($n = 12$), supine, standing and during treadmill walking, and the dose-response effects of two incremental doses (50 and 100mg) during sustained therapy ($n = 24$).

The control study began with a 10 minute period lying quietly at rest; heart rate (ECG) and blood pressure (random zero sphygmomanometer; Hawksey-Gelman; diastolic phase IV) were averaged from five recordings taken at minute intervals. The subjects then stood quietly at rest for two minutes following which five recordings were repeated at minute intervals. Finally, dynamic treadmill walking was undertaken for four minutes at a pre-determined speed and slope (3-4 mph; 10° incline) which had previously been found to induce an exercise tachycardia of 145 ± 5 bt/min in each subject. The acute study was undertaken in 12 subjects before and 3 and 24 hours after the first oral dose of 50 mg hydrochlorothiazide; the sustained effects of 50 and 100 mg were evaluated in all 24 subjects at the same times on completion of one month's treatment at each dose level.

Statistics

The statistical evaluation of circulatory variables was undertaken by analysis of variance, partitioning the variance between patients, treatment and time[4].

Results

The study was accomplished without untoward incident in any patient.

Acute Study ($n = 12$); (Table 1, Fig. 1).

At Rest. The only significant change was a reduction in supine systolic blood pressure ($P < 0.05$) at 24 hours after the first oral dose of 50 mg hydrochlorothiazide.

Table 1. Immediate circulatory effects of hydrochlorothiazide in essential hypertension (n = 12). Data are presented as mean \pm SEM. SBP—systolic blood pressure. DBP—diastolic blood pressure. HR—heart rate.

Posture	Variable	Control	Treatment (hours)	
			3	24
AT REST				
Supine	SBP	170 \pm 5	168 \pm 5	152 \pm 5*
	DBP	108 \pm 3	110 \pm 4	103 \pm 4
	HR	81 \pm 4	86 \pm 4	81 \pm 3
Standing	SBP	158 \pm 5	156 \pm 6	146 \pm 5*
	DBP	105 \pm 3	106 \pm 4	102 \pm 4
	HR	91 \pm 4	98 \pm 4	96 \pm 3
DURING EXERCISE				
1 min	SBP	190 \pm 6	185 \pm 7	185 \pm 8
	DBP	96 \pm 4	96 \pm 4	98 \pm 4
	HR	134 \pm 4	134 \pm 4	128 \pm 3*
2 min	SBP	207 \pm 7	200 \pm 8	194 \pm 8
	DBP	102 \pm 3	98 \pm 4	96 \pm 4
	HR	141 \pm 4	142 \pm 4	134 \pm 3*
3 min	SBP	211 \pm 7	201 \pm 8	203 \pm 8
	DBP	102 \pm 4	98 \pm 5	96 \pm 4
	HR	144 \pm 4	144 \pm 4	137 \pm 4*
4 min	SBP	209 \pm 7	207 \pm 8	205 \pm 7
	DBP	100 \pm 4	98 \pm 4	98 \pm 4
	HR	146 \pm 4	146 \pm 4	140 \pm 4*

*Tests of significance relate to drug versus control— $P < 0.05$

During Exercise. The absolute level of peak systolic blood pressure showed a tendency to fall both at 3 and 24 hours ($P < 0.1, > 0.5$); the increment from rest to exercise was unaffected. There were no changes in diastolic blood pressure. The absolute exercise heart rate and the increment from rest-to-exercise fell at 24 hours ($P < 0.05$).

Table 2. Circulatory effects of hydrochlorothiazide during sustained treatment in essential hypertension (n = 24). Data presented as mean \pm SEM. SBP—systolic blood pressure. DBP—diastolic blood pressure. HR—heart rate.

Posture	Variable	Control	Treatment			
			50 mg		100 mg	
			3 hours	24 hours	3 hours	24 hours
AT REST						
Supine	SBP	186 \pm 6	164 \pm 6***	166 \pm 6***	156 \pm 7***	163 \pm 7***
	DBP	114 \pm 3	105 \pm 4*	102 \pm 4*	102 \pm 4*	102 \pm 4*
	HR	81 \pm 5	88 \pm 3	82 \pm 4	85 \pm 4	86 \pm 4
Standing	SBP	172 \pm 5	151 \pm 5***	153 \pm 5***	145 \pm 8***	149 \pm 7***
	DBP	107 \pm 3	101 \pm 4	101 \pm 4	96 \pm 3*	97 \pm 3*
	HR	90 \pm 6	97 \pm 4	92 \pm 4	99 \pm 4	95 \pm 5
DURING EXERCISE						
1 min	SBP	207 \pm 7	183 \pm 7***	189 \pm 6***	184 \pm 9***	176 \pm 9***
	DBP	99 \pm 4	92 \pm 3*	93 \pm 3*	91 \pm 3*	92 \pm 3*
	HR	140 \pm 5	127 \pm 4**	128 \pm 3**	130 \pm 7**	129 \pm 5**
2 min	SBP	221 \pm 7	201 \pm 5***	201 \pm 6***	189 \pm 9***	196 \pm 8***
	DBP	106 \pm 3	93 \pm 4*	96 \pm 4*	94 \pm 3*	93 \pm 3*
	HR	145 \pm 5	132 \pm 4***	134 \pm 4**	132 \pm 6**	136 \pm 5**
3 min	SBP	227 \pm 6	206 \pm 6***	205 \pm 6**	192 \pm 5***	195 \pm 8***
	DBP	101 \pm 5	93 \pm 4*	93 \pm 4*	92 \pm 3*	94 \pm 3*
	HR	150 \pm 5	136 \pm 4**	136 \pm 3**	135 \pm 6**	141 \pm 4*
4 min	SBP	229 \pm 8	201 \pm 5***	212 \pm 5***	198 \pm 7***	201 \pm 9***
	DBP	99 \pm 5	92 \pm 3*	94 \pm 3*	91 \pm 3*	96 \pm 3*
	HR	152 \pm 5	139 \pm 4**	140 \pm 3**	136 \pm 6**	142 \pm 4*

Tests of significance relate to drug versus control—* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

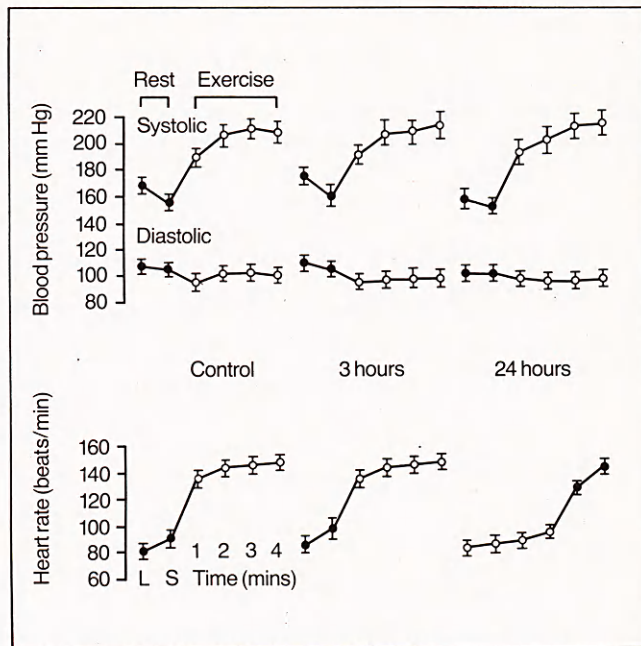


Fig. 1. Immediate circulatory effects of 50mg hydrochlorothiazide, at rest and during dynamic exercise, in 12 patients with essential hypertension. ●—at rest. ○—during exercise. I—SEM. L—lying. S—standing.

Chronic Study (n = 24); (Table 2, Fig. 2)

At Rest. Supine and standing, after one month's chronic treatment (50mg), the systolic ($P < 0.001$) and diastolic ($P < 0.05$) blood pressures were significantly reduced from control values; there was no significant difference

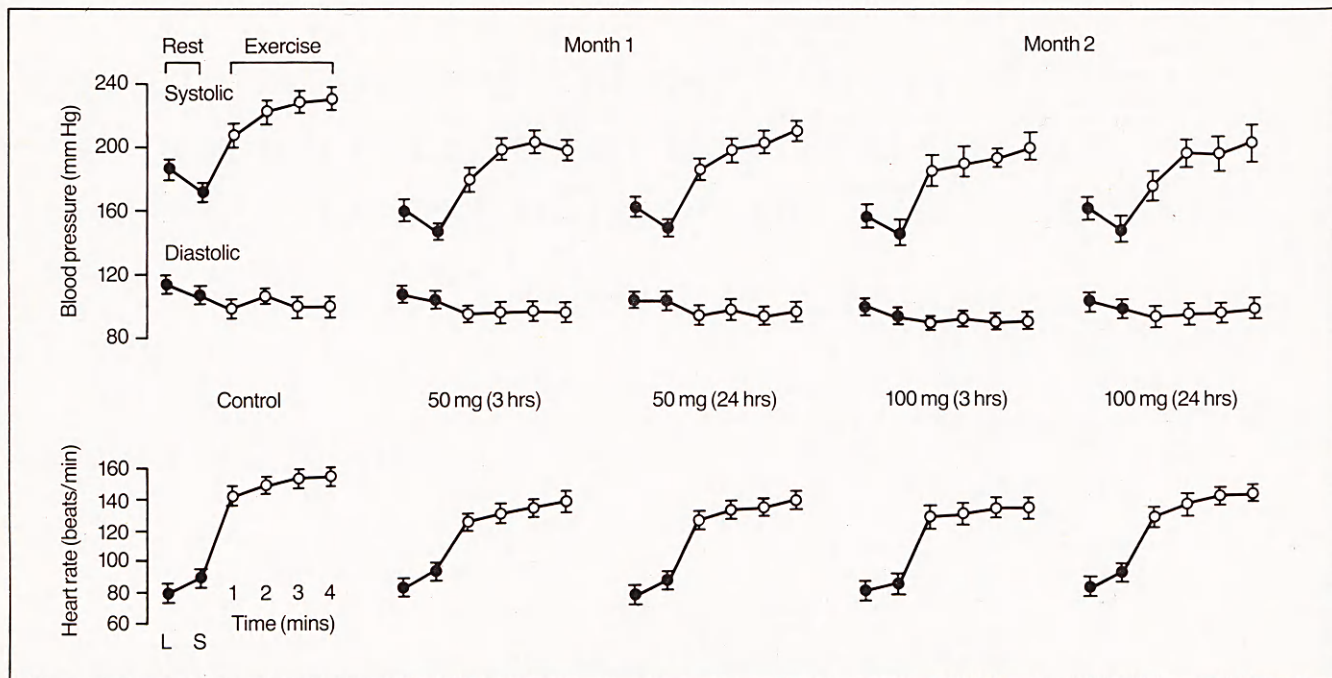


Fig. 2. Circulatory dose-response effects of 50mg and 100mg hydrochlorothiazide, at rest and during dynamic exercise, in 24 patients with essential hypertension. ●—at rest. ○—during exercise. I—SEM. L—lying. S—standing.

between the reductions at 3 or 24 hours. The heart rate was unchanged. After a further month's sustained therapy there were additional small reductions in blood pressure without change in heart rate.

During Exercise. Absolute systolic ($P < 0.001$) and diastolic ($P < 0.05$) blood pressures were reduced compared with control values at one month; there was no significant difference between the reductions at 3 or 24 hours. The absolute exercise heart rate and the rest-to-exercise increment ($P < 0.05$) were significantly reduced at both times from control values. After one month on 100mg there were small additional reductions in blood pressure without change in heart rate.

Discussion

Despite nearly three decades of clinical experience with the thiazide group of diuretics, their precise mode of action has not been unequivocally established[5]; the relative importance, from a mechanistic viewpoint, of their natriuretic[6-9] or vascular action[10-12] remains controversial. Nevertheless, the immediate and long-term haemodynamic effects of the thiazide group have been defined; on initiation of therapy a reduction in plasma and extracellular fluid volume is accompanied by a fall of central venous pressure with concomitant reduction in cardiac output and a rise in calculated peripheral vascular resistance[6,8,13,14]. During continued treatment, the initial reduction in cardiac output is reversed, with return to control pre-treatment level; the long-term anti-hypertensive action of the group results from a sustained reduction in peripheral vascular resistance[10].

The results of the present study confirm the extended

anti-hypertensive effectiveness of a single oral dose of hydrochlorothiazide over a 24-hour period; the blood pressure showed average reductions of 22/9 mm Hg at the 50 mg and 30/12 mm Hg at the 100 mg dose in the supine posture. These observations demonstrate the flat dose-response of the drug; the relatively small additional hypotensive effect from a doubling of the dose is in agreement with previous data[3]. During dynamic treadmill walking the reduction in the peak blood pressure was 28/7 mm Hg at the 50mg and 31/8 mm Hg at the 100mg dose, being of a similar order to the hypotensive effect at rest. It should be noted that the pressor response induced by dynamic exercise was unaffected by treatment; this contrasts with the observations of Varnauskas[2], although these findings are in agreement with other exercise data in essential hypertension[15].

An intriguing finding of the present study was the reduced absolute exercise tachycardia at the same workload in the initial 24 hour study and during sustained treatment. This reduction in exercise tachycardia suggests an improved cardiac performance which is probably consequent on a reduction in peripheral vascular resistance; the presence of the change as early as 24 hours after the first dose suggests an early reduction in peripheral vascular resistance consequent on thiazide therapy. Although many authors[13,14] have shown that the reduction in central venous filling pressure and cardiac output is the immediate circulatory adaptation to thiazides, many have misinterpreted the peripheral vascular effects at initiation of treatment; the reduction in cardiac output in relation to mean blood pressure has suggested an increased systemic vascular resistance. Nevertheless, the calculation of peripheral resistance assumes that the volume of blood in the arteries in relation to their

distensibility (i.e., volume/capacity/ratio) is unchanged[16]; clearly the natriuretic and vasodilator actions of the drug in decreasing intravascular volume while increasing effective capacity negates the simple and conventional approximation of the above formula (i.e., $PVR = \frac{BP}{CO}$).

Further support for this interpretation of the exercise data is provided by two reports. During an upright bicycle and graded exercise study in essential hypertension[2], it was observed that the increase in stroke volume from rest to two progressively higher workloads was +12 and +15 per cent in the control period, but +17 and +32 per cent following hydrochlorothiazide. This observation, together with the reduction in systemic arterial pressure at a given cardiac output, suggested that thiazides reduced peripheral vascular resistance at rest and augmented the reduction during exercise. These findings are compatible with those of Lund-Johansen[17], who demonstrated that the small reduction in resting blood flow following hydrochlorothiazide did not persist during dynamic exercise. The mechanism of the vascular action of the thiazide group is complex; the vascular responses to noradrenaline[18] and angiotensin II[19] are attenuated by therapy, and recent evidence has attributed the vasoactive properties of thiazides to an indirectly mediated increase in prostaglandin synthesis[20,21]. Nevertheless, the cause of the relative enhancement of the vascular action of thiazides during exercise is uncertain.

These studies have clarified aspects of the anti-hypertensive effectiveness of thiazides during dynamic exercise and have demonstrated that the single 50mg dose of hydrochlorothiazide gives sustained hypotensive action throughout the day; in most cases increasing to the 100mg dose confers little additional benefit. The hypotensive action of the drug applies equally at rest and during dynamic exercise; moreover, the circulatory adjustments to the latter are unimpaired by therapy.

Summary

The immediate and sustained circulatory effects of hydrochlorothiazide were evaluated at rest and during dynamic exercise in 24 patients with essential hypertension. Twenty-four hours after the first dose (50mg) there was a reduction in the resting systolic blood pressure, with attenuation of exercise tachycardia. During sustained therapy at two dose levels (50mg and 100mg), each of one month's duration, the systolic and diastolic blood pressure were reduced, both at rest and during dynamic exercise, without substantial difference between the two

doses. Exercise tachycardia was attenuated during long-term treatment, without alteration of the pressor responses to exercise. The reduction in exercise tachycardia at the same workload in this study suggests that thiazides, in addition to their diuretic action, have a vascular component that augments the fall in systemic vascular resistance during dynamic exercise.

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