

## Failure of anti-hypertensive drugs to control blood pressure rise with isometric exercise in hypertension

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### Summary

Isometric exercise causes a substantial rise in BP in normotensive and untreated hypertensives. The authors studied the isometric hand-grip test in 5 groups of treated hypertensives, namely  $\beta$ -blockers,  $\beta$ -blockers + diuretics,  $\beta$ -blockers + diuretics + vasodilators,  $\alpha$ -methyldopa alone and labetalol. All groups showed a substantial rise in both systolic and diastolic BP, and the increments in BP differed little from that in normotensives. Some patients, despite multiple therapy, achieved increments of up to 60 mmHg from rest. Treated hypertensives with cardiac and cerebro-vascular disease are at risk performing isometric exercise.

### Introduction

Isometric (static) exercise causes a substantial rise in systolic and diastolic BP in both normotensive and untreated hypertensive subjects (Hoel, Lorentsen and Lund-Larsen, 1970; Ewing *et al.*, 1973). In patients with left ventricular impairment due to hypertension, coronary artery and other heart disease, isometric exercise can cause angina (Cohn *et al.*, 1973), dangerously elevated left ventricular end-diastolic pressure (Cohn *et al.*, 1973; Kivowitz *et al.*, 1971; Helfant, de Villa and Meister, 1971), gallop rhythms (Fisher *et al.*, 1975) and arrhythmias (Cohn *et al.*, 1973). BP during isometric exercise can be extremely high in hypertensives, yet there are few studies on the effect of various anti-hypertensives in this area (Editorial, 1975).

In normotensives,  $\beta$ -blockers alone and  $\alpha$ -blockers (Martin *et al.*, 1974), are ineffective. In hypertensives, prazosin and propranolol (Reuben, Gale and Blake 1979) used separately are ineffective in attenuating the BP rise in isometric exercise. The authors have studied the pulse and BP changes in 47 hypertensives to determine which of 5 different drug regimes attenuate the BP rise seen with isometric exercise.

### Patients and methods

The isometric hand-grip test was used in a standardized manner after Ewing *et al.* (1974), using

a mercury sphygmomanometer (Taylor, Belfield and Taylor, 1978). The subject squeezed the partially inflated cuff at 30% of his maximum voluntary contraction until fatigue forced him to release his grip. This took a mean of 3 min (range 2-5 min). The pulse and BP (diastolic fifth phase) were measured on the non-exercising arm, before the test, one-min intervals, and at the point of fatigue.

The 47 hypertensives, 32 male and 15 female, with a mean age of  $43 \pm 16$  years were on treatment for at least 3 months. None of the patients was in cardiac failure. Five treatment groups were studied: group A ( $n=9$ ) patients on  $\beta$ -blockers alone, 7 were on propranolol and 2 on oxprenolol, mean daily dose  $196 \pm 121$  mg; group B ( $n=17$ ) patients on  $\beta$ -blockers + diuretics, 14 were on propranolol, mean daily dose  $200 \pm 96$  mg, 9 were on thiazides and 5 on metolazone, 3 were on frusemide; group C ( $n=10$ ) patients on  $\beta$ -blockers + diuretics + vasodilators, 8 were on propranolol, mean daily dose  $430 \pm 208$  mg, 4 patients were on thiazides, 4 were on metolazone and 3 on frusemide, 5 patients were on hydralazine, mean daily dose 160 mg, 2 were on diazoxide, mean 360 mg/day and 2 were on prazosin, mean 15 mg/day; group D ( $n=6$ ) patients on  $\alpha$ -methyldopa, mean daily dose 1000 mg/day; group E ( $n=5$ ) patients on labetalol, mean daily dose 1100 mg/day, 4 of these were also on thiazide diuretics.

Twenty-four medical personnel, 12 male and 12 female, not on any medication acted as controls. Reasons for exclusion before admission to the study were: atrial fibrillation (because of difficulty measuring BP accurately) disability of the exercising limb and those with advanced renal failure (serum creatinine  $>600 \mu\text{mol/l}$ ) as this impairs the BP response in the test (Ewing and Winny, 1975). The BP response with isometric exercise is greater in males than in females (Freychus, 1970). A similar though statistically not significant, trend in the controls was noted. Treatment groups were statistically compared with the appropriate control group according to sex distribution, using unpaired Student's *t* tests.

TABLE 1. Control subjects, BP mean ( $\pm$ s.d.) in mmHg, and pulse, mean ( $\pm$ s.d.) at rest and at fatigue after 30% maximum voluntary contraction

No. of patients	Resting BP		Fatigue BP		Rise in BP		Pulse		Pulse rise
	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Rest	Fatigue	
Male (12)	133 (15)	82 (10)	159 (11)	111 (13)	26 (12)	30 (15)	73 (10)	84 (10)	13 (6)
Female (12)	123 (11)	72 (7)	141 (15)	95 (13)	18 (9)	23 (8)	84 (14)	107 (23)	21 (15)
M+F (24)	128 (14)	77 (10)	150 (16)	103 (16)	22 (12)	27 (13)	79 (13)	103 (13)	19 (13)

\* Systolic BP rise M > F, ( $t=1.455$ ),  $P=0.0796$ .

† Diastolic BP rise M > F, ( $t=1.282$ ),  $P=0.106$ .

**Results**

Table 1 shows the BP and pulse changes in the control subjects—the changes were similar to previous reports in normotensive subjects (Martin *et al.*, 1974; Ewing *et al.*, 1974).

Figure 1 and Table 2 show the BP and pulse responses of the 5 treatment groups. There was a substantial rise in both systolic and diastolic BP in all groups. The incremental rise in systolic BP in the 5 treatment groups was  $\geq$  than controls, i.e. there

was no significant attenuation of systolic BP rise. A mild attenuation of the diastolic BP rise was obtained in groups B and D. Four hypertensives achieved systolic BP levels over 240 mmHg, 9 achieved diastolic BP levels of over 140 mmHg, and 4 had an incremental rise of 60 mmHg in the systolic BP from rest. The resting pulse rate in patients on  $\beta$ -blockers was lower than that in controls (reflecting compliance with therapy). The rise in pulse rate with isometric exercise was mildly

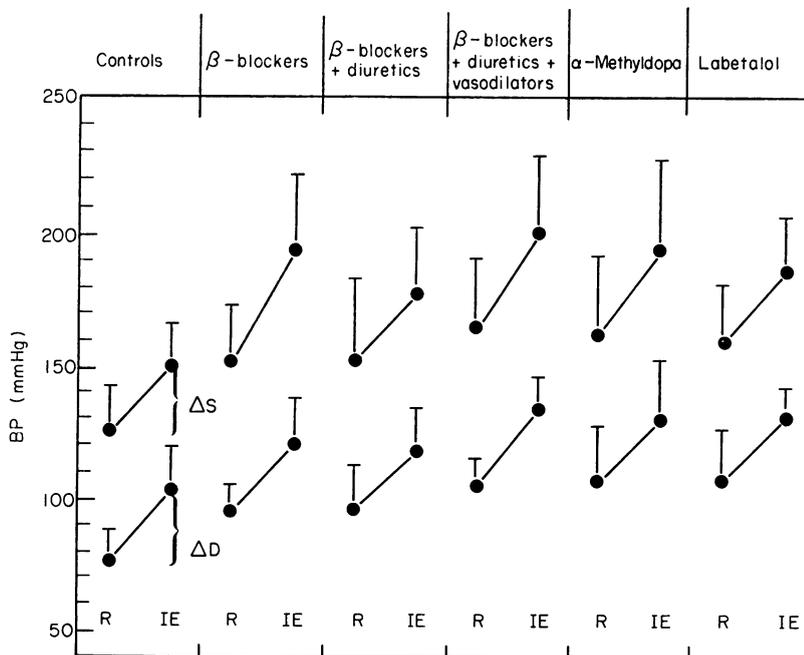


FIG. 1. Mean BP ( $\pm$ s.d.) at rest and at fatigue point at 30% maximum voluntary contraction for controls (combined male and female) and 5 treatment groups.

$\Delta$ S=mean increment of systolic BP and  $\Delta$ D=mean increment of diastolic BP. R=rest; IE=isometric exercise.

TABLE 2. Hypertensives: blood pressure in mmHg, mean ( $\pm$ s.d.) and pulse mean ( $\pm$ s.d.) changes from rest and fatigue at 30 maximum voluntary contraction. Group A:  $\beta$ -blockers alone; Group B:  $\beta$ -blockers+diuretics; Group C:  $\beta$ -blockers+diuretic + vasodilators; Group D:  $\alpha$ -methyldopa; Group E: labetalol.

Group	Sex		Resting BP		Fatigue BP		Rise in BP		Significance of BP rise v. controls:		Pulse		Sig. pulse rise from controls:	
	M	F	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	Rest	Fatigue		Pulse rise
A*	6	3	153 (18)	96 (9)	195 (26)	122 (15)	42 (12)	28 (10)	NS	NS	65 (9)	78 (8)	11 (9)	NS
B†	9	8	154 (27)	97 (14)	178 (24)	117 (15)	24 (16)	20 (9)	NS	$P < 0.05$	65 (8)	75 (12)	10 (8)	$P < 0.01$
C*	10	0	166 (24)	106 (8)	199 (30)	134 (11)	35 (13)	28 (11)	NS	NS	67 (7)	80 (13)	13 (9)	NS
D*	5	1	162 (30)	109 (19)	193 (34)	130 (23)	28 (11)	18 (16)	NS	$P < 0.02$	82 (15)	104 (19)	22 (10)	NS
E†	3	2	159 (21)	108 (18)	184 (22)	130 (11)	25 (14)	22 (11)	NS	NS	76 (11)	93 (9)	18 (17)	NS

\* Statistical comparisons made with male controls. † Statistical comparisons made with male+female controls.

attenuated in all patients on  $\beta$ -blockers ( $P < 0.01$  in group B). None of the patients suffered clinically apparent adverse effects during the tests.

### Discussion

The authors have demonstrated the failure of some of the most commonly used anti-hypertensive drugs in therapeutic doses, both alone and in combination, appreciably to attenuate the substantial rise in BP seen in isometric exercise. The magnitude of the BP rise in normotensives and hypertensives has previously been shown to be similar, but hypertensives achieve higher absolute BP levels, (Hoel *et al.*, 1970; Ewing *et al.*, 1973). A systolic BP  $> 240$  mmHg or a diastolic BP  $> 140$  mmHg was recorded in 12 patients, despite treatment with multiple drug therapy sufficient to attain reasonable steady state BP levels.

The mechanism of the BP rise in untreated subjects is well understood. For the BP rise to be significant, the subject must exercise at greater than 20% of the maximum voluntary contraction of the muscle group used and, as fatigue develops, the BP rises steadily (Lind *et al.*, 1964). In normotensive and hypertensive subjects without left ventricular impairment, the BP rise is due to increased cardiac output (Martin *et al.*, 1974), initially by withdrawal of vagal tone and, as fatigue develops, by cardiac sympathetic drive; peripheral resistance usually remains unchanged. However, if the subject has left ventricular impairment (Ewing *et al.*, 1973), or is on  $\beta$ -blockers (Martin *et al.*, 1974), the BP rise is mainly by increased peripheral resistance mediated by  $\alpha$ -adrenergic receptors (Martin *et al.*, 1974). Thus, it is possible to interpret the action of various anti-hypertensives in isometric exercise.

Previous studies have been with single drug therapy only. Beta-blockers (Reuben *et al.*, 1979; Taylor, Belfield and Taylor, 1978) as well as  $\beta$ -blockers (Freychus, 1970; Reuben *et al.*, 1979), ineffective in attenuating BP rise. In their patients the present authors also demonstrated the effectiveness of  $\beta$ -blockers alone. They therefore studied the effects of additional therapy with diuretics which, besides causing a natriuresis, probably also have a direct effect on the arteriolar wall reducing peripheral resistance (Jones and Nanra, 1979). The result was a modest ( $P < 0.05$ ) attenuation of the diastolic rise in BP only, compared to controls. However, when vasodilators were combined with diuretics and  $\beta$ -blockers (group C) the expected further attenuation of the BP rise was not seen. Indeed, the systolic and diastolic BP increments with exercise were greater than those in group B, although similar to those in controls. These findings could not be explained by inadequate drug dosage as the mean daily dose of propranolol (450 mg) was higher than in groups A and B, and the diuretics and vasodilators were used in standard or maximum doses. Patients on  $\alpha$ -methyldopa showed no systolic and mild diastolic attenuation of BP response. The latter is surprising as  $\alpha$ -methyldopa is not thought to act on the peripheral autonomic nervous system where the links in this reflex could be acted on. However,  $\alpha$ -methyldopa could diminish peripheral resistance through damping of the central sympathetic mechanisms (Nickerson and Riedy, 1975). The failure of labetalol, which has both  $\alpha$ - and  $\beta$ -blocking properties during dynamic exercise (Fagard *et al.*, 1979), should theoretically block the 2 major pathways which mediate the BP rise to isometric exercise. The mean daily dose was 1100 mg which

corresponds to an average therapeutic dose, and one patient who was on 2400 mg/day still had a rise in BP similar to that in controls. The heart rate rise on labetalol was 18 beats/min, confirming the findings in a recent study (Balasubramanian *et al.*, 1979), which showed that labetalol does not give complete  $\beta$ -blockade at normal doses. However, none of the drugs, including  $\beta$ -blockers, can prevent the initial rise in pulse that is mediated by vagal withdrawal, which increases cardiac output and thus allows some BP escape. Furthermore, it would seem that vasodilators, which reduce steady state peripheral resistance, cannot sufficiently attenuate the sudden and severe demands of the sympathetic nervous system in isometric exercise.

Besides the cardiovascular hazards outlined earlier, isometric exercise has been associated with subarachnoid haemorrhage (Lynch, 1980), and may increase the risk of other cerebro-vascular accidents, both during isometric exercise and in the long-term, by increasing the daily time-averaged arterial pressure (Ewing *et al.*, 1973). Thus, the authors advise patients to avoid unnecessary isometric exercise in work and recreation. Alternatively, they advise patients to re-distribute loads to larger muscle groups (Ewing *et al.*, 1975), e.g. carrying a load on the back rather than by hand, as strain is less and fatigue reached more slowly, thereby avoiding substantial rises in BP.

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