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THE EFFECTS OF α- AND β-ADRENERGIC RECEPTOR BLOCKERS ON THE PRESSURE RESPONSES TO ISOMETRIC EXERCISE IN HYPERTENSIVE PATIENTS

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1 The cardiovascular responses to handgrip exercise have been studied in ten patients with uncomplicated essential hypertension in a randomized crossover study of propranolol and prazosin.

2 Isometric handgrip exercise was performed with a calibrated strain gauge dynamometer at 30% of maximum voluntary contraction for 3 min.

3 Blood pressure and heart rate were measured in the supine position at rest and in the last 10 s of the exercise period.

4 These exercise studies were undertaken at the end of a run-in period and at the end of 1 month's optimal therapy with the two drugs.

5 The active treatment periods were separated by a 2 weeks placebo washout period.

6 Both drugs lowered the supine and standing systolic and diastolic pressures and there was no difference between these drugs in their effect on these variables.

7 Propranolol lowered the resting heart rate and neither drug suppressed the pressor response to isometric exercise.

8 The degree of pressure rise was similar with both drugs but propranolol suppressed isometric exercise-induced tachycardia.

Introduction

Isometric or static exercise is performed as part of many daily activities (holding or carrying objects, working with the arms overhead). Studies in healthy subjects have shown that sustained isometric exercise results in a highly significant rise in systemic blood pressure and heart rate (Lind, Taylor, Humphreys, Kennelly & Donald, 1964; Donald, Lind, McNicol, Humphreys, Taylor & Staunton, 1967; Lind & McNicol, 1967). In patients with left ventricular myocardial disease, sustained isometric handgrip exercise has been shown to evoke or accentuate haemodynamic evidence of cardiac dysfunction (Helfant, de Villa & Meister, 1971; Siegel, Gilbert, Nutter, Schlant & Hurst, 1972; Fisher, Nutter, Jacobs, & Schlant, 1973; Hume, Irving, Kitchin & Reuben, 1975).

We were interested to examine the heart rate and blood pressure responses to isometric handgrip exercise of a group of patients with essential hypertension and to assess any modification of the response by therapy with an α- or β-adrenoceptor blocking agent in an attempt to elucidate the reflex pathways involved.

Methods

Ten newly-presenting patients with uncomplicated essential hypertension, aged between 21 and 57 years, gave informed consent to participate in the study. The study started with a run-in period of 2 weeks so that supine and erect blood pressure was recorded on three occasions. The patients were admitted to the study if the supine pressure was 150/100 mm Hg or more. The blood pressure throughout the study was measured by one observer using an Accoson (Hospital Model) sphygmomanometer. The diastolic blood pressure throughout the study was taken as Korotkoff phase 4. Isometric handgrip exercise was performed with a calibrated strain-gauge dynamometer and the patient's maximum voluntary contraction (MVC) was first determined. The patients

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then maintained 30% of their MVC for 3 min. A standard electrocardiogram (ECG) was recorded throughout for heart rate determination. The patients were instructed not to hold their breath and they were carefully observed for signs of hyperventilation. The blood pressure was recorded in the non-exercising arm in the last 10 s of the exercise period.

The patients were then randomized to initial therapy with either the post-synaptic α-adrenoceptor blocker, prazosin (Hypovase) or the β-adrenoceptor blocker, propranolol (Inderal). Prazosin was commenced in a dose of 0.5 mg three times daily, the patients being instructed to take the first dose about 1 h before retiring to bed to avoid possible 'first dose effects'. The patients randomized to propranolol were given the drug in a dose of 80 mg three times daily. All patients were seen at weekly intervals and the blood pressure and heart rate was recorded both in the erect and supine position. The target blood pressure for optimal treatment was taken as a diastolic pressure of less than 95 mm Hg.

Prazosin therapy was increased by 0.5 mg three times daily each week and propranolol by 80 mg per day, each week until an optimal fall in pressure was achieved. The patients were then maintained on the optimal dose of either drug for a period of 1 month and then isometric handgrip exercise was repeated using the same protocol as for the control observations. The patients then received a placebo washout preparation taken thrice daily for a period of 2 weeks. At the end of this placebo washout period, resting and isometric exercise blood pressure and heart rate were obtained. The patients were finally crossed over to the second active drug and the dose schedule described and titrated to an optimal blood pressure response. After 1 month's therapy on the second drug at optimal dose the resting and exercise blood pressure and heart rate responses were recorded.

Results

Statistical analysis was performed by the paired *t*-test method and the group mean data and s.d. for the resting blood pressure and heart rate during the run-in and treatment periods are shown in Table 1. It can be seen that both prazosin and propranolol produced an insignificant postural effect. The average dose of prazosin to produce this optimal blood pressure response at rest was 4.5 mg per day and propranolol 320 mg per day. Propranolol produced the expected fall in resting heart rate and prazosin therapy resulted in no significant alteration in this variable. When the prazosin data was compared with that for the propranolol period, only heart rate was significantly different ($P<0.001$).

The isometric exercise data is shown in Table 2 and it can be seen that this form of exercise produced a highly significant rise in heart rate and systolic blood

Table 1 Resting blood pressure and heart rate (mean ± s.d.)

	Supine systolic blood pressure (mm Hg)	*Supine diastolic blood pressure (mm Hg)*	*Supine heart rate (beats/min)*	*Erect systolic blood pressure (mm Hg)*	*Erect diastolic blood pressure (mm Hg)*
Run-in	167±10.2	108±4.0	84±7.7	162±6.0	106±4.9
Prazosin	141±10.4	87±3.5	83±6.7	136±9.9	87±5.0
	$P<0.001$	$P<0.001$	NS	$P<0.001$	$P<0.001$
Propranolol	131±9.6	85±4.3	64±7.0	129±11.7	88±2.6
	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$

Table 2 Exercise blood pressure and heart rate (mean ± s.d.)

	Systolic blood pressure (mm Hg)	*Diastolic blood pressure (mm Hg)*	*Heart rate (beats/min)*
Run-in	191±21.9	116±9.6	101±14.3
Prazosin	164±22.6	103±10.3	93±13.2
	$P<0.001$	$P<0.001$	NS
Propranolol	149±22.7	97±10.9	67±10.0
	$P<0.001$	$P<0.001$	$P<0.001$

pressure during the run-in period. Diastolic blood pressure rose by 8% but this was less significant. Neither prazosin nor propranolol blocked the pressor response to handgrip exercise. The exercise systolic blood pressure rose 16.6% during prazosin therapy and 14% on propranolol, there being no significant difference between the two group mean levels. It is interesting that the percentage rise in diastolic pressure during handgrip was greater on both therapies. Propranolol completely blocked the heart rate response and prazosin attenuated it so that the rise was only 11.5% compared to 20% in the control period. As with the resting data the only difference between the response on prazosin as compared to propranolol was the effect on exercise heart rate.

Discussion

Although isometric exercise is a common component of daily activities and the pressor and tachycardia responses well documented (Lind *et al.*, 1964; Donald *et al.*, 1967; Lind & McNicol, 1967), the reflex mechanisms responsible for the changes are incompletely understood. McDonald, Sapru, Taylor & Donald (1966) examined the effects of intravenous propranolol on the responses in seven healthy volunteers and found that there was no change in the increase in mean aortic pressure during handgrip after the drug, but that the cardiac output response was reduced and was compensated by increased systemic vascular resistance. These workers found rather surprisingly, that the percentage increase in heart rate during handgrip after intravenous propranolol was greater than in the control situation. Martin, Shaver, Leon, Thompson, Reddy & Leonard (1974) have also examined the autonomic mechanisms involved in the haemodynamic responses to isometric exercise in normal volunteers and have used intravenous propranolol and the cardioselective β-adrenoceptor blocker, practolol, to block the β sympathetic nervous system and intravenous atropine to block the parasympathetic nervous system. They found that the initial 30 s of the tachycardia response was mediated by withdrawal of vagal tone, but the later portion of the tachycardia response was sympathetic in origin, being blocked by the combination of intravenous atropine and propranolol. They demonstrated that the pressor response to handgrip was accompanied by increased cardiac output and no change in calculated systemic vascular resistance. However, after propranolol, handgrip resulted in increased peripheral resistance and an equivalent rise in arterial pressure but no increase in cardiac output. The response was the same after intravenous practolol suggesting that the change in peripheral vascular resistance was independent of peripheral β-adrenergic receptors.

Previously Freyschuss (1970) had examined the effects of giving atropine and phentolamine individually and then in combination on the heart rate and blood pressure response to isometric exercise in healthy volunteers. She found that atropinization inhibited the tachycardia response but the pressure rise was maintained. Phentolamine had no effect on the heart rate response but the pressure elevation was diminished. The combination of atropine and phentolamine markedly reduced the heart rate and the blood pressure response to isometric handgrip exercise. She concluded that the tachycardia response to isometric exercise was initiated by a release from vagal tone and that the pressure rise could be ascribed both to a heart rate acceleration and to an effect on the systemic vascular resistance mediated by the alpha-adrenergic receptors of the sympathetic nervous system.

Ewing, Irving, Kerr & Kirby (1973) examined the cardiovascular responses to isometric exercise in a group of hypertensive patients and found that they could be divided into two groups. The first group responded by an increase in cardiac index and heart rate with little or no change in systemic vascular resistance. These patients thus conformed to the pattern of response observed in normal subjects (Martin *et al.*, 1974). The second group of patients responded by an increase of systemic vascular resistance, a smaller rise in heart rate and little or no change in cardiac index. These patients had either electrocardiographic or radiographic evidence of left ventricular hypertrophy, suggesting that the differences in response was due to impaired left ventricular function.

It would seem unlikely that the results of studies from normal volunteers can be readily extrapolated to explain the behaviour of a heterogeneous group of hypertensive patients. Studies using isometric exercise as a stress test in the cardiac catheterization laboratory have demonstrated a wide range of responses of left ventricular filling pressure, contractility and cardiac output in patients with varying degrees of left ventricular dysfunction on other criteria (Helfant *et al.*, 1971; Hume *et al.*, 1975).

Although the patients in the present study had no clinical, electrocardiographic or radiological evidence of left ventricular hypertrophy it cannot be assumed that left ventricular function in response to an isometric stress test would be normal. Furthermore, it is highly likely that the results of studies using intravenous propranolol in normal volunteers are quite different from those obtained in hypertensive patients on chronic oral dosage. Certainly the patients in this study had a completely blocked heart rate response to isometric exercise whilst on propranolol therapy and this is at variance with the experience of MacDonald and co-workers (1966) and Martin and colleagues (1974). These latter workers

have suggested that part of the pressor response to handgrip is due to an increased peripheral resistance resulting from sympathetically induced vasoconstriction.

This study is interesting in that prazosin, which is a post-synaptic α-adrenoceptor blocking drug had no significant effect on the systolic pressure response to isometric exercise. This may be because the alpha-adreno-receptors are not involved in the reflex in hypertensive patients despite the observations made by Freyschuss (1970) in acute studies in normal volunteers, or alternatively the reflex may only involve the pre-synaptic α-adrenoceptors of the sympathetic nervous system and prazosin has been shown to be a post-synaptic α-adrenoceptor blocking drug.

The present study raises interesting points in the management of patients with hypertension. The prognostic importance of a raised systolic blood pressure at rest has been widely recognized from epidemiological studies and there are now many drugs which can effectively lower resting blood pressure. It is also recognized that β-adrenoceptor blocking drugs can successfully attenuate the pressor response to dynamic exercise (Epstein, Robinson, Kahler & Braunwald, 1965). However, the present study has failed to show attenuation of the pressor response to isometric exercise by two currently available drugs which lower the arterial pressure by acting on the sympathetic nervous system in quite different ways. The significance of a treated hypertensive patient periodically producing hypertensive levels of pressure in response to static exercise is unknown but the work of Sokolow, Werdegar, Kain & Hinman (1966) would suggest that the time-averaged arterial pressure for the day is related to the cerebrovascular complications of hypertension. Isometric handgrip exercise could provide a simple test to help in the titration of an individual patient's treatment so that the peak systolic pressor response to the stress was maintained with a normotensive range.

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