

THE HÆMODYNAMIC EFFECTS OF β -SYMPATHETIC BLOCKADE

BY

D. A. CHAMBERLAIN AND JANE HOWARD

From the Department of Cardiology, Saint Bartholomew's Hospital, London E.C.1

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Ahlquist (1948) postulated that sympathetic receptor sites were of two types, which he called α and β , and this concept has been supported by other workers. Most of the sympathetic excitatory effects depend on α -receptors, and the inhibitory effects on β -receptors. One important exception is the heart, where stimulation is a β -adrenergic action. The older adrenergic-blocking drugs are known to inhibit only the α -receptors, and this explains their failure to influence sympathetic control of the myocardium. The first drug capable of β -adrenergic blockade was dichloroisoprenaline (D.C.I.) (Powell and Slater, 1958), but this was by no means free of sympathomimetic action of its own (Furchgott, 1959; Dresel, 1960; Black and Stephenson, 1962). Pronethalol is a similar agent, with little sympathomimetic activity. It was originally described under the provisional official name of nethalide by Black and Stephenson (1962). Like D.C.I. it bears a structural resemblance to isoprenaline (Fig. 1).

The drug has been used in the present study to investigate the effects of sympathetic blockade of the heart on the hæmodynamics of exercise.

SUBJECTS AND METHOD

Ten normal volunteer medical students, 9 men and 1 woman, were studied; their ages ranged from 20 to 27 years. Observations of cardiac output, heart rate, and blood pressure were made at rest and on treadmill exercise on two separate occasions: once without medication, and once after the administration of pronethalol. Before the tests, each student was made familiar with the cardiac laboratory and with the techniques used. The order in which the experiments were performed was alternated so that with five subjects the observations after pronethalol were made first.

The cardiac output estimations were made using a dye-dilution technique with the Cambridge earpiece and mark-2 recorder. Nylon catheters of 1.02 mm. internal diameter were introduced percutaneously over a Seldinger guide wire into antecubital veins, one in each arm, and passed about 18 in. (46 cm.) to bring them near the origin of the superior vena cava. One was used for injections of 2 per cent Coomassie blue, and the other, with multiple side-holes near the tip, for obtaining samples of venous blood. Blank and tail specimens were obtained for each curve because, when using an earpiece, calibration does not remain constant with changes in posture or on exercise. Arterial sampling was found to be unnecessary provided adequate time was allowed for complete mixing. Good baselines during exercise could be obtained by careful attention to stability of the earpiece on the ear: this was achieved by fitting a pad of polyester foam around the earpiece, and securing the pad with a *crêpe* bandage. Adequate earthing of both the patient and the recorder was also important. There was often a slight phasic respiratory artefact of the baseline, especially during exercise, but not enough to affect the validity of the calculations. In several subjects it was necessary to administer oxygen to prevent variations in arterial saturation causing unacceptable baseline instability. Some examples of exercise curves are shown (Fig. 2).

Heart rates were recorded by means of a Sanborn direct-writing electrocardiograph with two electrodes held in place by a single strap around the chest. Blood pressures were measured using a sphygmomanometer

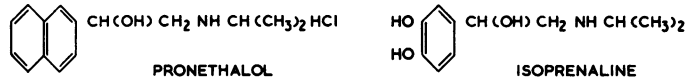


FIG. 1.—Chemical structure of pronethalol.

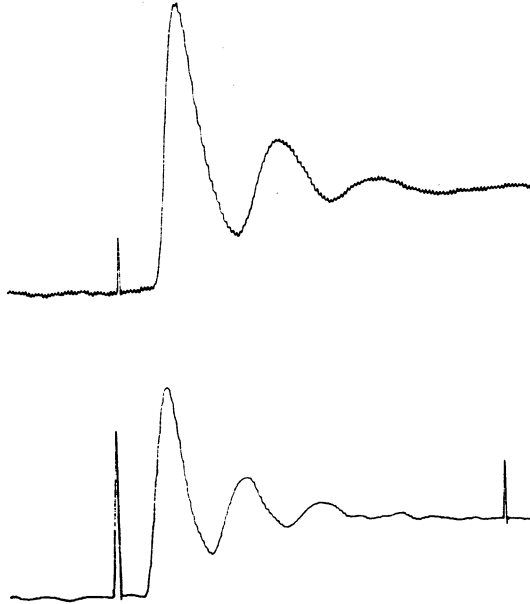


FIG. 2.—Examples of dye curves recorded from an earpiece during treadmill exercise.

TABLE I

EFFECTS OF PRONETHALOL UPON HEART RATE AND CARDIAC OUTPUT IN TEN NORMAL SUBJECTS (SUPINE)

Subject	Heart rate (beats/min.)		Cardiac output (l./min.)	
	Control	Pronethalol	Control	Pronethalol
1	57	51	6.7	6.4
	55	55	5.1	6.9
2	68	69	5.5	5.8
	70	66	4.9	5.9
3	52	45	6.8	6.3
	53	47	7.9	5.7
4	63	61	6.7	6.8
	57	63	6.2	7.0
5	59	62	5.6	7.9
	57	68	5.6	7.5
6	75	69	8.1	8.6
	73	70	6.5	8.4
7	70	62	6.5	7.0
	68	60	6.2	6.6
8	65	65	6.9	6.3
	61	61	6.6	6.7
9	70	62	4.3	4.3
	69	—	4.4	—
10	61	55	6.1	6.2
	60	54	6.4	6.3

cuff, with a stethoscope diaphragm held over the brachial artery on the left antecubital fossa by *crêpe* bandage.

For each experiment, measurements of cardiac output, heart rate, and blood pressure were made twice with the subjects supine, once standing, and once at the end of the third minute of walking on the treadmill at 2.5 m.p.h. up a 7° gradient. In addition, heart rates and blood pressures were recorded at half-minute intervals during exercise, and for four minutes subsequently. The mean of the two supine outputs was accepted; the average variation was nearly 10 per cent on the control day but only 5 per cent after pronethalol.

The drug was always given orally and observations then made in the period one to two and a half hours afterwards. All but two subjects were given 200 mg.: the exceptions were made for one particularly heavy student, and for one particularly light student, who were given 300 and 150 mg. respectively.

RESULTS

At Rest. Comparison of the data obtained with and without the drug (Table I) shows that pronethalol had little influence on the hæmodynamics in the supine position. The heart rate was appreciably decreased in only 4 subjects, and in none by more than eight beats per minute. The effect on cardiac output was small, the figure on the pronethalol day being slightly higher in 6 subjects and within 20 per cent of the control in all but one. There was an increase in stroke volume in 8 of the 10 students; averaged for the series, the increment was 12 per cent. Changes in blood pressure were small and inconstant.

There were wide fluctuations in blood pressure on standing, irrespective of medication; this influenced heart rate, and made it difficult to achieve valid baselines with the earpiece. Pronethalol exerted no effect which could be detected under these circumstances.

TABLE II
CARDIAC OUTPUT AFTER THREE MINUTES OF STANDARD EXERCISE BEFORE AND AFTER PRONETHALOL

Subject	Control	Pronethalol
1	20.4	17.2
2	11.6	10.9
3	17.0	14.8
4	14.5	14.0
5	10.7	15.5
6	14.9	13.6
7	16.1	16.6
8	15.5	15.1
9	13.9	9.9
10	14.2	12.9

On Exercise. Calculations of cardiac output before and after pronethalol were made in all 10 subjects studied (Table II), records of heart rate during and after exercise were obtained in 9, and it was possible to obtain reliable blood pressure measurements in only 8. The most consistent change was in pulse pressure. In every case where observations were made, there was a narrower pulse pressure during the exercise following pronethalol; but this was not usually so in the four-minute period afterwards. The averaged pulse pressures recorded on the two occasions are shown in Fig. 3: the graph for any of the individuals studied would be similar. The response of systolic and diastolic pressures was more variable, but in most cases the systolic fell slightly and the diastolic rose, so that mean pressure remained almost unchanged.

All but one student (Subject 5) had less tachycardia during exercise after taking pronethalol, and also in all but one the heart rate fell more rapidly in the four-minute period after walking. The difference averaged approximately 10 beats a minute during the exercise and up to 20 beats a minute afterwards (Fig. 4), but there was considerable individual variation.

Despite the slower heart rate and decreased pulse pressure observed after the drug, there was

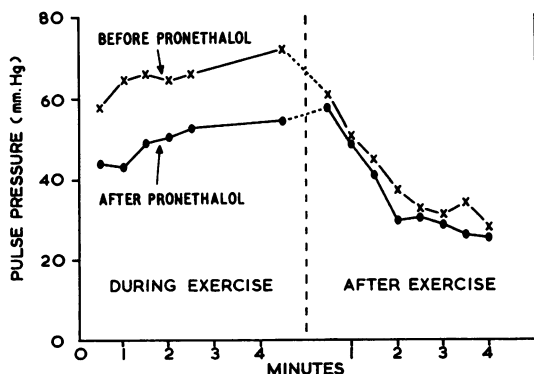


FIG. 3.—Averaged pulse pressures recorded during and after exercise.

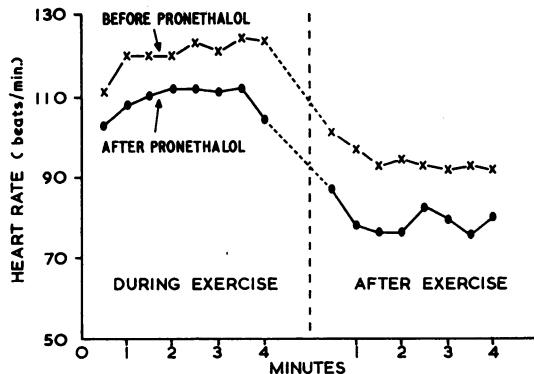


FIG. 4.—Averaged heart rates recorded during and after exercise.

found to be relatively little change in the cardiac output of exercise in most of the students. The one large increase in output on pronethalol occurred in Subject 5, in whom all outputs were considerably higher on the day the drug was given. Another showed a very slight increase, but 8 had falls ranging from 3 per cent to 29 per cent. In 6 students the difference in calculated output on exercise before and after pronethalol did not exceed 10 per cent, and this change can hardly be considered significant. Calculated stroke volume fell in 2, was identical in 1, and rose in 7 subjects. Averaged for the series, there was an increase of 5 per cent.

DISCUSSION

Pronethalol had little influence on the increased cardiac output of exercise; in most subjects the change in output after the drug was not outside the limits of experimental error. This is in agreement with the findings of Dornhorst and Robinson (1962) in their observations on two normal subjects. There was less tachycardia in response to standard exercise after the drug, a finding compatible with the blockade of the positive chronotropic effects of sympathetic stimulation. The slowing of the heart rate was more significant than any reduction in cardiac output, so that average stroke volume was actually increased.

The consistently smaller pulse pressure observed during exercise after pronethalol was therefore surprising. This was not due to peripheral factors, because there was little change in mean pressure or resistance. An alternative explanation is that the rate of systolic ejection might have been slower: when the same amount of blood is ejected in a longer time, the amplitude of the pulse wave will clearly be decreased. Sarnoff *et al.* (1960) have shown, in an anesthetized dog, that stellate ganglion stimulation reduced the duration of ventricular systole by 23 per cent while the heart was paced at a constant rate. Conversely, abolition of inotropic sympathetic effects on the heart would be expected to prolong ejection time. The suggestion that pronethalol does produce this effect is in keeping with its proven action as a β -adrenergic blocking agent, and has already been demonstrated in experimental animals (Black and Stephenson, 1962). The reduction in pulse pressure observed in the present experiments implies a similar action in man. There is therefore evidence that both the chronotropic and the inotropic effects of sympathetic stimulation were blocked by pronethalol; in spite of this, the cardiac output of exercise was almost unchanged, with the reduction in heart rate partly compensated by an increased stroke-volume in most subjects.

This finding provides good evidence that sympathetic influences are not of prime importance in maintaining an increased cardiac output during exercise. The chief function of sympathetic control may be in protecting the ventricles from the greater end-diastolic pressure and fibre length that would otherwise result from the increased venous return. However, before firm conclusions can be

drawn, it will be necessary to make observations of cardiac output at different degrees and different stages of exercise, and in cases where β -adrenergic blockade can be shown to be complete.

The small effect of pronethalol on the circulation in resting healthy subjects is to be expected, because under these conditions there is relatively little sympathetic influence on the heart. It cannot be assumed that the same would apply to patients with heart failure, in whom the sympathetic drive may constitute an important compensatory mechanism.

SUMMARY

The hæmodynamic effects of a β -adrenergic blocking agent, pronethalol, have been studied. It has little effect in healthy resting subjects. On exercise, any reduction in cardiac output is small, but it does reduce heart rate so that stroke volume may be increased. There is a reduction in pulse pressure on exercise, and it is postulated that this is due to increased ejection time.

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