Haemodynamic studies in hypertensive patients treated by oral propranolol

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Haemodynamic studies have been performed in 9 patients whose blood pressures had been satisfactorily controlled with oral propranolol for 7 to 29 months. A postural drop of blood pressure or a fall of blood pressure on exercise did not occur. Pulse rate and cardiac output were below normal at rest and on exercise; peripheral resistance was high. The results are similar to those obtained in a comparable group of hypertensives after acute administration of propranolol. These findings are discussed in relation to the mode of action of propranolol in hypertension.

The β -receptor blocking drug propranolol is an effective drug in the treatment of systemic hypertension (Prichard and Gillam, 1964, 1969; Tewari and Grant, 1968; Frohlich *et al.*, 1968). The intravenous administration of propranolol to patients with systemic hypertension produces a significant fall of cardiac output supine (Ulrych *et al.*, 1968), erect, and on exercise (Shinebourne, Fleming, and Hamer, 1967). In the present investigation a group of hypertensive patients effectively controlled by long-term oral propranolol was studied to determine the haemodynamic effect of therapy. Measurements were made at rest and during exercise on a treadmill.

Methods

Nine volunteer patients with hypertension (six essential, three renal), from the series of Prichard and Gillam (1969), were investigated. Clinical details with levels of blood pressure in outpatients on previous treatment are given in Table 1. These patients were taking regular oral propranolol to reduce the diastolic pressures, supine and standing, to the range 80 to 100 mm. Hg. The dose used in these patients varied from 160 to 1150 mg. daily, given in four doses. Five of these patients also received a diuretic.

The haemodynamic studies were made at least seven months after control of the blood pressure with propranolol. The experimental procedure has been described previously (Hamer, Fleming, and Shinebourne, 1967). Under local anaesthesia, polythene catheters were passed

percutaneously by the Seldinger technique into the left basilic vein and right brachial artery. Direct intra-arterial pressures were recorded using a P23Gb strain gauge transducer (Statham Laboratories) and a Devices direct writing recorder. Cardiac output was measured by an indicator dilution technique, using indocyanine green with a Gilford densitometer and the dynamic method of calibration.

Measurements were made supine at rest, standing, and while walking on the treadmill at 3 m.p.h., on the flat, and at slopes of 3°, 6°, and 9°, in patients able to exercise at this level; no rest periods were allowed between the various levels of exercise. The haemodynamic measurements were made at a steady state after four minutes of exercise.

The systemic resistance was calculated as the mean arterial pressure in mm. Hg, divided by the cardiac output in litres per minute. The pressure-time per minute was derived from the product of the ejection time (i.e. onset of the arterial pressure wave to the dicrotic notch), mean ejection pressure, and heart rate. Ejection rate was calculated by dividing the stroke volume by the ejection time.

Results

The effect on blood pressure is seen in Table 2 and Fig. 1. There is little change of blood pressure on standing, but the normal tendency to a reduction in pulse pressure remains. Systolic pressure rises significantly on exercise, but the diastolic pressure does not exceed the resting standing level until the highest exercise load is reached. The pulse rate (Table 2 and Fig. 2) shows a gradual rise as the exercise level is increased.

The resting, standing, and exercise cardiac outputs are low (Table 3 and Fig. 3).

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TABLE 1 Out-patient blood pressure readings

Case No., sex, age (yr.)	Fundus	ECG	Urea (mg./100 ml.)	Pre-treatment supine blood pressure (mm. Hg)	Previous treatment blood pressure (mm. Hg)		Dose (mg./day)	Propranolol ‡ Blood pressure (mm. Hg)		Dose (mg./day)	Months of treatment
					Supine	Standing		Supine	Standing		
Bethamidine											
1 M 44	IV	LV+	36	290/170	184/113§	120/89	90†	140/85	116/89	400†	8
2 M 28	II	LV+	34	215/150	210/218	146/107	1000†	146/72	132/92	1150†	15
3 M 44	II	LV+	35	210/155	176/104	135/89	85†	143/86	151/95	400†	7
Reserpine											
4 F 67	II	LV+	44	200/125	155/95	140/90	0.25	149/88	150/85	240†	24
Methyldopa											
5 M 52	III	LV+	52	220/160	180/130	155/130	750	132/101	109/94	200†	19
6 M 47	I	LV+	28	180/130	115/75	110/80	1750	112/80	110/80	240	24
7 M 38	I	LV+	31	*	135/90	135/95	750	119/94	105/80	160	25
8 M 44	II	LV+	45	180/140	148/104	136/102	1000†	150/90	130/98	800	8
9 M 44	I	—	33	230/135	120/70	105/75	2250	128/76	130/90	160	25

* No pre-treatment figures available.

† With a diuretic.

‡ Out-patient readings at time of haemodynamic studies.

§ Blood pressure readings taken by London School of Hygiene and Tropical Medicine sphygmomanometer; hence no digit preference or rounding off of figures.

Peripheral resistance is high, rises on standing, and then falls progressively on exercise (Table 4 and Fig. 4). Pressure-time per minute and ejection rate (Table 5, Fig. 5 and 6) are low in the supine position, fall further on standing, and increase on exercise.

Discussion

The treadmill offers a natural form of exercise, but has the disadvantage that the work

load cannot be measured precisely. Since a heavier person must do more work for a particular setting, no correction for body size was made. Once patients start to exercise, effects of anxiety or other stimuli are largely abolished, and at four to six minutes, when measurements are made, a steady state is reached.

Our results (Table 2, Fig. 1) confirm, as reported previously (Prichard and Gillam,

TABLE 2 Blood pressure and heart rate

Case No.	Supine Syst. diast.	Pulse rate	Erect Syst. diast.	Pulse rate	3 m.p.h. 0° Syst. diast.	Pulse rate	3 m.p.h. 3° Syst. diast.	Pulse rate	3 m.p.h. 6° Syst. diast.	Pulse rate	3 m.p.h. 9° Syst. diast.	Pulse rate
1	170/85	48	195/100	43	180/95	75	195/105	85	200/105	91	225/115	109
2	135/80	58	140/90	59	165/90	90	170/90	100	170/95	114	180/100	121
3	150/75	54	150/85	67	185/80	80	190/90	97	205/100	115	225/105	139
4	135/60	65	135/65	64	200/85	100	180/80	105	195/80	114	215/95	123
5	130/75	56	100/60	65	120/65	78	120/65	89	125/55	109		
6	150/95	71	140/95	74	145/80	93	130/65	115	140/70	134	140/75	146
7					110/80	84	140/65	107	135/75	136	135/75	150
8	175/100	54	170/110	64	205/100	90	205/100	100	225/105	119	200/100	123
9	145/75	69	150/85	77	175/85	120	160/80	120	155/80	128		
Mean:	149/81	59	148/87	64	165/84	90	165/82	102	172/85	118	189/95	130
S.E.	5.8 4.5	2.9	9.7 6.0	3.7	11.2 3.4	4.6	10.2 5.2	3.8	11.8 5.7	4.6	14.5 5.8	5.7

Values of *p* difference between systolic pressure: Erect-Exercise 0°, *p* < 0.02; 3°-6° slope, *p* < 0.10; diastolic pressure: 6°-9° slope, *p* < 0.05; pulse rate: Erect-Exercise and 3°-6° slope, *p* < 0.001; 0°-3° slope and 6°-9° slope, *p* < 0.005. All other differences, *p* > 0.10. Probabilities calculated from differences in logarithms of blood pressure (or pulse rate) of patients compared.

FIG. 1 Blood pressure (bars indicate standard error of mean).

FIG. 4 Peripheral resistance (bars indicate standard error of mean).

FIG. 2 Heart rate (bars indicate standard error of mean).

FIG. 5 Pressure-time per minute (bars indicate standard error of mean).

FIG. 3 Cardiac output (bars indicate standard error of mean).

FIG. 6 Ejection rate (bars indicate standard error of mean).

1969), that in patients whose blood pressure is lowered by propranolol there is no further fall in pressure on standing or on exercise, in contrast to the response seen when the pressure has been lowered by bethanidine, guanethidine, or methyldopa (see Prichard, 1969). The rise in peripheral resistance on standing (Table 4 and Fig. 4) is further evidence that the sympathetic nervous control of blood vessels is unaffected by propranolol.

The results of the present study are consistent with inhibition of cardiac sympathetic activity. The blood pressure is near to the normal at rest, both supine and standing, and rises slowly on exercise, the main change being in the systolic component. The heart rate is slow and the cardiac output is correspondingly reduced both at rest and during exercise.

Shinebourne *et al.* (1967) reported the effect of acute administration of propranolol to hypertensive patients. Systolic blood pressure was significantly reduced at rest supine and standing, and the rise of systolic pressure on exercise was reduced. Diastolic blood pressure was not significantly reduced in supine and standing positions, but the diastolic pressure on exercise after propranolol was lower than before propranolol administration. Ulrych *et al.* (1968), studying the effect in the supine position, found no hypotensive action from acute administration of propranolol. This is in contrast to the marked hypotensive effect of prolonged oral treatment with propranolol which we have observed. However the dosages in the acute studies of Shinebourne *et al.* (1967) (1 mg./kg. i.v.), and Ulrych *et al.* (1968) (10 mg. i.v.), are not necessarily comparable to the dosage used in the prolonged oral studies. The heart rate (Table 2, Fig. 2), pressure-time per minute (Table 5, Fig. 5), ejection rate (Table 5, Fig. 6), and cardiac output (Table 3, Fig. 3) at rest and on exercise after oral propranolol are slightly lower than was found in the comparable group of untreated hypertensives after intravenous propranolol (Shinebourne *et al.*, 1967).

Prichard and Gillam (1964, 1969) have drawn attention to the difference between acute and prolonged oral effects of propranolol. Though there is maximal bradycardia within 24 hours of a constant oral dose, the hypotensive effects seem to increase over a period of up to two months though the greater fall is in the first one or two weeks. The intravenous administration of propranolol is associated with at most a moderate hypotensive effect due to a fall in cardiac output,

TABLE 3 Cardiac output at rest and on exercise

Case No.	Supine	Erect	Exercise 3 m.p.h. walking on treadmill			
			0°	3°	6°	9°
1	3.3	2.4	5.6	7.8	8.1	10.3
2	3.9	3.1	6.5	7.9	9.2	9.7
3	3.9	2.8	6.0	7.6	9.6	12.8
4	3.3	2.3	4.5	5.3	5.4	6.0
5	3.2	2.1	5.9	6.6	8.1	
6	3.7	2.8	6.5	7.9	10.0	10.9
7			8.7	7.3	8.3	10.9
8	4.1	2.6	7.4	8.5	10.3	11.0
9	6.2	4.6	11.5	11.2	12.5	
Mean	4.0	2.8	6.9	7.8	9.1	10.2
	p < 0.01	p < 0.001	p < 0.05	p < 0.005	p < 0.01	
S.E.	0.34	0.28	0.68	0.53	0.65	0.79

(Values of p calculated as in Table 2.)

TABLE 4 Peripheral resistance at rest and on exercise (mean arterial pressure/cardiac output in l./min.)

Case No.	Resting supine	Erect	Exercise 3 m.p.h. walking on treadmill			
			0°	3°	6°	9°
1	34	52	22	17	17	15
2	25	33	17	15	13	13
3	26	38	20	16	14	12
4	26	39	27	22	22	23
5	32	39	15	14	11	
6	33	41	17	12	9	9
7			10	12	12	9
8	32	52	18	15	14	12
9	16	23	10	10	8	
Mean	28	40	17	15	13*	13
	p < 0.001	p < 0.001	p < 0.05	p < 0.02	*p < 0.01	
S.E.	2.13	3.36	1.81	1.16	1.41	1.81

* Mean of 7 patients at 6° slope able to exercise at 9°, 14.

(Values of p calculated as in Table 2.)

TABLE 5 Derived indices of left ventricular performance at rest and on exercise

	Supine	Erect	Exercise 3 m.p.h. walking on treadmill			
			0°	3°	6°	9°
Pressure-time/min. (mm. Hg sec./min.)						
Mean	2650	2500	3750	4150	4700	5500
	p < 0.60	p < 0.05	p < 0.10	p < 0.005	p < 0.01	
S.E.	160	160	530	280	400	340
Ejection rate (ml./sec.)						
Mean	200	165	240	250	290	284
	p < 0.10	p < 0.02	p < 0.10	p < 0.025	p < 0.80	
S.E.	16	13	31	17	20	31

(Values of p calculated as in Table 2.)

with a rise in peripheral resistance from compensatory haemostatic reflexes. The fall in cardiac output is partially but not entirely (Shinebourne, 1969) rate-dependent. The absence of progressive fall in pulse rate suggests that the gradual fall in blood pressure with prolonged oral propranolol is not due to a progressive fall in cardiac output.

Prichard and Gillam (1964, 1969) have postulated that propranolol reduces the cardiac component of various stimuli responsible for transient rises in blood pressure; for instance it reduces the overshoot of blood pressure after Valsalva's manoeuvre. It was suggested that the baroreceptors are gradually conditioned, by the damping down of pressure responses, to regulate the blood pressure at a lower mean level. The peripheral resistance of these patients being treated with chronic oral propranolol is similar to that found by Shinebourne *et al.* (1967) with acute propranolol, and does not suggest any progressive fall. However, these findings were in different patients, and the problem will not be resolved until the response to intravenous and chronic oral propranolol is studied in the same subjects.

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