Effects of propranolol on response to exercise in hypertrophic obstructive cardiomyopathy

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The circulatory, respiratory, and metabolic responses to steady state submaximal exercise have been studied in four women and two men with hypertrophic obstructive cardiomyopathy, before treatment, after intravenous, and after three months of oral propranolol.

The physical working capacity was significantly lower than in normal subjects, and the response to exercise was characterized by a tachycardia, low cardiac output and stroke volume, and high ventilation and blood lactate concentration. After propranolol there was a significant reduction in heart rate, but changes in most other measurements were slight and there was no improvement in effort tolerance though angina was relieved in the two patients in whom it was present. The possible causes of breathlessness and effort intolerance in hypertrophic obstructive cardiomyopathy are discussed in relation to known effects of propranolol. It is concluded that further trial of propranolol and other beta-adrenergic blocking agents is warranted.

Breathlessness, angina, syncope, and arrhythmias are common features of hypertrophic obstructive cardiomyopathy which are exaggerated by exercise (Goodwin, 1967). Therapeutic measures should relieve these symptoms, protect against occasionally fatal complications, and ideally halt or reverse the usually progressive nature of this disease. Because of the possibility of excessive catecholamine stimulation of the heart, beta-adrenergic blockade was introduced for the treatment of this disorder (Cherian *et al.*, 1966), and this form of treatment has subsequently been evaluated by others (Cohen and Braunwald, 1967; Sloman, 1967; Flamm, Harrison, and Hancock, 1968).

After beta-adrenergic blockade with propranolol angina is frequently relieved but breathlessness has been found to persist with little or no improvement in effort tolerance (Goodwin, 1970). Protection against exercise syncope or arrhythmias may be conferred but this is as yet unproven. We felt it was important to determine the effects of beta-adrenergic blockade on cardio-respiratory function during exercise in view of the

many unanswered questions regarding the value and indications for this mode of treatment. Furthermore, previous exercise studies in patients with hypertrophic obstructive cardiomyopathy have concentrated on investigating the haemodynamic abnormality (Braunwald *et al.*, 1964); in this study we describe the interrelated cardiovascular, respiratory, and metabolic responses to graded submaximal exercise, together with the effects on these responses of acutely and chronically administered propranolol.

Patients and methods

Four young women and two men were studied. They had symptoms of dyspnoea, angina, or syncope of 1–4 years' duration, and all had the physical signs of hypertrophic obstructive cardiomyopathy as described by Goodwin (1967). The diagnosis was confirmed by electrocardiographic, radiological, and angiographic investigations. Haemodynamic studies showed resting left ventricular outflow tract gradients of 40–79 mm. Hg in three patients and 0–13 mm. Hg in the remaining three patients. Left atrial mean pressure exceeded 12 mm. Hg in four patients.

The respiratory, circulatory, and metabolic responses to exercise were studied before starting treatment, later the same day after intravenous propranolol (0·1 mg./kg. body weight), and, finally, after at least three months oral propranolol (240 mg./day in all except one patient (Case 1) in whom the maximum tolerated dose was 60 mg./day).

So that type of exercise should be comparable to that experienced in ordinary life, subjects exercised in the upright position on an electrically stabilized load cycle ergometer. Full resuscitation measures were close at hand. A preliminary, bloodless, exercise test was done in which the power load was increased from rest by 100 kpm./min. each minute while the electrocardiogram, heart rate, and ventilation were recorded continuously and the patient's clinical response noted. This procedure ensured that near maximal exercise could be tolerated safely, familiarized the patient with the technical procedures, and enabled the physical working capacity at a pulse rate of 170 per minute (PWC_{170}) to be estimated by close intra– or extrapolation of the linear pulse work relation (Sjöstrand, 1960).

A polythylene catheter (PE60) 22 cm. long was introduced percutaneously into the brachial artery under local anaesthesia using a modified Seldinger technique (Bernéus *et al.*, 1954). Intravascular pressures were measured with a saline-filled variable inductance manometer (Elema), the linearity and calibration of which was checked before and after each study. The reference zero for intravascular pressure measurements was the sternal end of the fourth rib when the patient was seated in the exercising position.

A low dead space low resistance respiratory valve was used; expired gas passed continuously through a Tissot spirometer which served as a mixing chamber except when timed gas collections were made. Expired gas was sampled at either the lips (tidal gas) or distal to the Tissot spirometer (mixed expired gas) and analysed with an infra-red CO_2 meter (Godart URAS), having 95 per cent confidence limits of ± 0.1 per cent and a paramagnetic oxygen meter (Servomex DCL) having 95 per cent confidence limits of ± 0.05 per cent. Heart rate was recorded using electrocardiograph electrodes placed anteroposteriorly over the apex beat. Electrical outputs from the Tissot spirometer potentiometer, CO_2 meter, electrocardiograph, and haemodynamic manometer were recorded with a direct-writing oscillograph (Mingograf 81) which also enabled mean pressures to be estimated by electrical integration.

Blood sampled in heparinized glass syringes was analysed immediately for Pco_2 with a Severinghaus electrode, Po_2 by a Beckman macroelectrode, and total plasma CO_2 (TCO_2) by a Natelson microvolumetric apparatus, the 95 per cent confidence limits being ± 0.8 mm. Hg for Pco_2, ± 0.72 mm. Hg for Po_2, and 0.3 mM/l. for TCO_2, respectively. Arterial blood samples for lactate estimations were drawn in less than 15 seconds into dry syringes and immediately deproteinized with 5 per cent w/v perchloric acid. Samples were refrigerated until analysed by a modified enzymatic technique (Hohorst, 1957) using standard reagents (C. F. Boehringer, U. Soehne, Mannheim, W. Germany). Duplicate analyses of lactate concentration showed mean differences of 0.112 ± 0.17 mm./l.

The partial pressures of CO_2 in oxygenated mixed venous blood were estimated by a rebreathing technique (Jones *et al.*, 1967). From values for arterial Pco_2 and mixed venous Pco_2, the veno-arterial CO_2 content difference was obtained using relationships developed by McHardy (1967), and the cardiac output was calculated using Fick's equation. A comparison between cardiac output measurements made in this way and those with indicator dilution techniques has been reported (Higgs *et al.*, 1967).

After making measurements of ventilation, gas exchange, blood gases, blood lactate, and brachial arterial pressures at rest, the patient exercised at one or more submaximal power loads. Continuously recorded heart rate, end-tidal, and expired gas concentrations allowed recognition of a steady state as defined by Jones *et al.* (1966). This was generally achieved by the end of the third minute when formal measurements of intravascular pressures were followed by simultaneous collections of expired gas and arterial blood for one minute and the subsequent measurement of the oxygenated mixed venous Pco_2 by rebreathing. A blood sample for lactate estimation was taken at 6 minutes, after which exercise was either stopped or continued at a higher level.

When the heart rate had returned to the pre-exercise level after exercise, propranolol was given intravenously over 20 minutes while the electrocardiogram and brachial arterial pressures were monitored continuously: exercise was then repeated on the same day and subsequently on oral therapy at the same levels sustained previously.

Residual 'anatomical' shunt was estimated from the alveolar to arterial Po_2 difference after 10 minutes breathing 100 per cent oxygen at rest.

The cardiovascular, respiratory, and metabolic responses to exercise in these patients have been compared with those of similarly aged normal sedentary subjects studied in this laboratory (Higgs *et al.*, 1967; Hughes *et al.*, 1968; H. M. Pope, B. E. Higgs, and M. Clode, unpublished observations) and with published normal data (Sannerstedt, 1966).

Standard statistical programmes using a digital computer (Elliott 4100) facilitated data analysis.

Results

Physical working capacity at a heart rate of 170 beats/min. (PWC_{170}) before treatment (Table 1) was lower than the individual normal controls ($PWC_{170} = 1037 \pm SD = 224$ kpm./min. for male subjects (Edwards *et al.*, 1969) and $635 \pm SD = 105$ kpm./min for female subjects (Pope *et al.* unpublished report).

The highest exercise levels sustained for 6 minutes before treatment were low, reflecting reduced working capacities. After propranolol the same work levels were sustained but with complaints of greater fatigue. Measurements of forced expired volume in

TABLE I *Anthropometric, clinical, and haemodynamic data*

	Case Nos.					
	1	*2*	*3*	*4*	*5*	*6*
Sex	F	F	F	F	M	M
Age (yr.)	20	21	25	22	33	21
Height (cm.)	158	153·5	158	162	185	176
Weight (kg.)	52·2	51·5	44·5	55·5	73·3	67·7
$FEV_{1·0}$ (l.)	3·1	2·3	2·5	2·6	4·9	4·55
Vital capacity (l.)	3·6	2·8	3·1	3·6	6·3	5·1
Haemoglobin (g./100 ml.)	12·3	12·5	10·2	13·7	13·3	14·7
PWC_{170} (kpm./min.)	385	375	340	440	780	760
Symptoms	Angina	Dyspnoea	Dyspnoea	Dyspnoea, angina	Dyspnoea, syncope	Dyspnoea, syncope
Duration (yr.)	2	1	3	3	4	4
LA mean pressure (mm. Hg.)	11	18	12	19	19	13
LV pressure (mm. Hg)	125/0–11	145/7–25	186/18–26	100/18–26	144/8–16	174/6–16
Aortic pressure (mm. Hg)	120/50	132/80	107/69	100/66	90/64	134/96
LV outflow gradient (mm. Hg)	5	13	79	0	54	40

the first second (FEV1·0) and vital capacity (VC) were within the normal range (Cotes, 1965); there was no change in either measurement after propranolol.

The effects of propranolol on heart rate, cardiac output, systemic vascular pressures, ventilation, and arterial lactate concentration are shown in Fig. 1–6, respectively. Each patient is represented by a different symbol. The results for men and women are compared with the appropriate control values (mean ± 1 SD). Main columns refer to power load, the column labelled 'B' referring to results before treatment, 'I.V.' and 'O' being the results after intravenous or three months' oral propranolol, respectively.

Heart rate Resting heart rate after intravenous propranolol was 6–8 beats lower, but the difference was not statistically significant.

When patients were restudied on oral propranolol, the resting heart rate was 10 beats/min. lower than before treatment (p < 0·01). On exercise the heart rate tended to be greater than normal at a given power load after treatment (Fig. 1). There were significant reductions of 30 beats/min. (p < 0·00001), and 37 beats/min. (p < 0·001) after propranolol administered intravenously or orally, respectively. No cardiac arrhythmias were encountered.

Cardiac output This rose less in these patients than in controls (Fig. 2) and was not appreciably affected by propranolol. Calculated stroke volumes were uniformly low and there was little change after intravenous or

oral propranolol, values being on average 55 per cent (±SD = 15) and 64 per cent (±SD = 10) of mean normal controls, respectively. Low cardiac outputs implied wide arteriovenous oxygen content differences and low mean mixed oxygen saturations (corresponding to 50%, 40%, and 47% of mean normal controls, respectively). Brachial artery systolic and mean pressures (Fig. 3 and 4) increased less on exercise than would have been expected from a comparison with normal subjects (Sannerstedt, 1966). After propranolol variable slight falls in brachial artery mean pressure were observed in most subjects (Fig. 4). Mean estimates of cardiac

FIG. I *Changes in heart rate on exercise before (B) and after intravenous (I.V.) and oral (O) propranolol in relation to normal responses (mean ± 1 SD).* ● *Case 1;* ▲ *Case 2;* ○ *Case 3;* △ *Case 4;* ■ *Case 5;* □ *Case 6.*
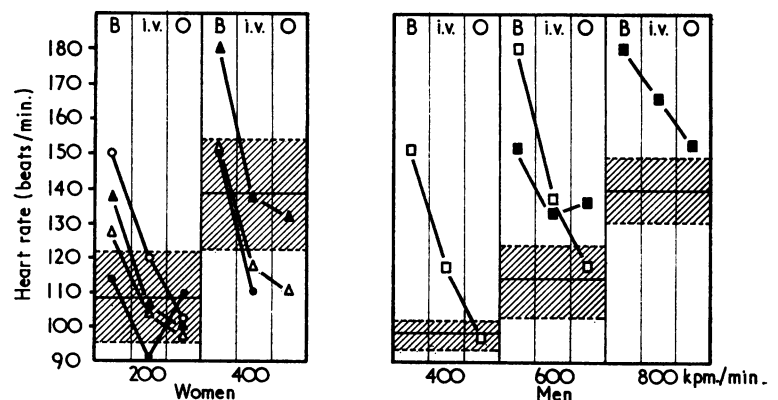
work rates calculated as cardiac output (1./min.) × brachial artery mean pressure mm. Hg, were 896 ± SD = 306, 753 ± SD = 231, and 856 ± SD = 435, l./mm. Hg/min. before treatment and after intravenous and oral propranolol, respectively. A significant (p < 0·05) reduction in cardiac work was seen only after intravenous propranolol.

Ventilation This tended to be high on exercise (Fig. 5) especially at a patient's highest work load. The effects of propranolol were small and inconsistent. Arterial gas tensions, venous admixture effect, dead-space/tidal volume, ratio, and respiratory frequency at each individual's highest exercise level before treatment are shown in Table 2. Simliar results were found after intravenous and oral propranolol.
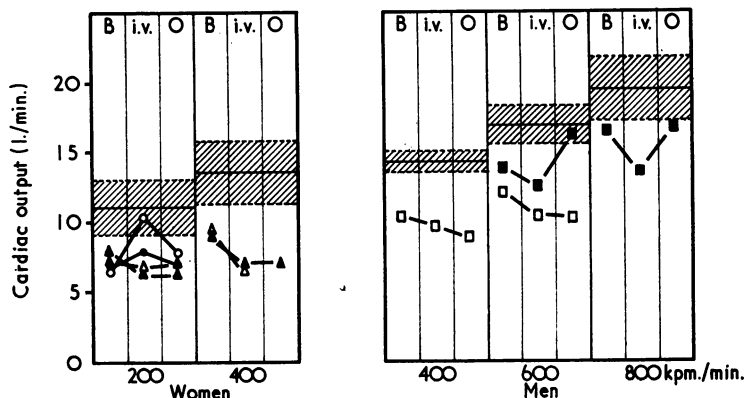

FIG. 2   *Changes in cardiac output on exercise. Symbols as in Fig. 1.*

TABLE 2   *Respiratory responses at highest exercise level before propranolol*

Case No.	Maximum power load (kpm./min.)	Arterial P_{CO_2} (mm. Hg)	Arterial P_{O_2} (mm. Hg)	'Ideal' alveolar to arterial P_{O_2} difference (mm. Hg)	Venous admixture effect (% of cardiac output)	Dead-space/tidal volume ratio	Respiratory frequency (breaths/ min.)
1	200	31·5	86·0	29·0	4·7	0·21	25
2	400	36·5	82·5	37·0	4·8	0·16	35
3	200	25·0	101·5	22·0	6·5	0·17	31
4	400	32·0	87·5	28·0	3·5	0·06	32
5	800	32·5	77·5	35·5	4·4	0·33	44
6	600	28·5	100·5	24·0	1·8	0·23	46

Arterial lactate concentration increased excessively on exercise in all but one subject, and was similarly raised after intravenous and oral propranolol (Fig. 6).

The alveolar to arterial P_{O_2} difference while breathing 100 per cent O_2 indicated that anatomical right-to-left shunting was within normal limits. Changes in arterial hydrogen ion and bicarbonate concentrations were consistent with the presence of a lactacidosis and alveolar overventilation in all except Case 2, and the effects of propranolol were small and inconsistent.

In general, the performance on exercise of the three patients with large outflow tract gradients (Table 1) did not differ from others with little or no gradient, and there was no evidence of a different effect of propranolol in the former group.

Discussion

The patients studied had complaints that were largely related to effort intolerance. Objective measurements showed lower work-

FIG. 3   *Changes in brachial arterial systolic and diastolic pressures on exercise. Symbols as in Fig. 1.*
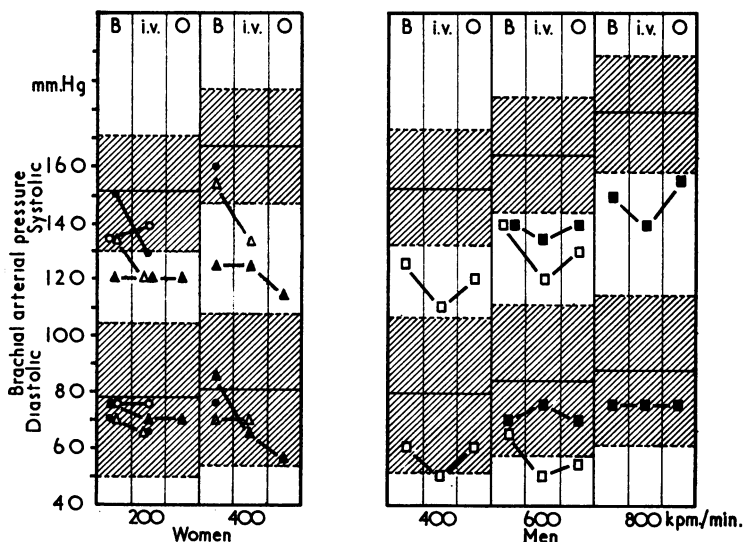
ing capacities than in comparable normal subjects.

In normal subjects exercise is usually limited by the capacity of the peripheral circulation to adapt rather than to a limitation of ventilation or pulmonary gas transfer (Asmussen, 1965). In our patients with hypertrophic obstructive cardiomyopathy the principal abnormal responses to exercise can also be related to the cardiovascular system. There were excessive increases in heart rate, subnormal cardiac output responses, and consistently low stroke volumes. Though none of our patients fainted or became hypotensive during exercise, the rise in systolic and mean brachial arterial pressures was less than in normal subjects (Sannerstedt, 1966), and this was due largely to a low cardiac output; the calculated total peripheral resistance being normal. Low arterial Po_2 values and alveolar to arterial differences (Table 2), which were greater than those found in normal subjects by Filley, Gregoire, and Wright (1954) and Jones *et al.* (1966), might suggest an impairment of pulmonary gas transfer, possibly due to ventilation-perfusion imbalance as in mitral stenosis (Dollery and Hugh-Jones, 1963). Calculated venous admixture ratios were close to those found in normal subjects (Jones *et al.*, 1966). Physiological dead-space/tidal volume ratios during exercise (those at the highest exercise level being shown in Table 2) were somewhat larger than those found in normal women by Pope *et al.* (unpublished) and in normal men by Jones *et al.* (1966). However, they are probably not grossly abnormal in view of the high respiratory frequencies observed in all except Case 1 (Table 2). The finding of near normal venous admixture and dead-space/tidal volume ratios suggests that ventilation-perfusion imbalance in the lungs, if it exists, is not severe in our patients but it might exist in other patients with hypertrophic obstructive cardiomyopathy especially if pulmonary vascular congestion were present. The reduced arterial oxygen tensions that we observed can be attributed to a near normal degree of admixture of venous blood ('physiological shunting') having a very low oxygen saturation as a direct consequence of the low cardiac output.

A low cardiac output also results in reduced transport to the exercising muscles, a problem potentially exaggerated by low arterial oxygen tensions or haemoglobin concentrations (as in Cases 3 and 5). Using the rise in arterial lactate concentration as an indication of the extent to which oxygen supply falls short of demands (Wasserman, Van
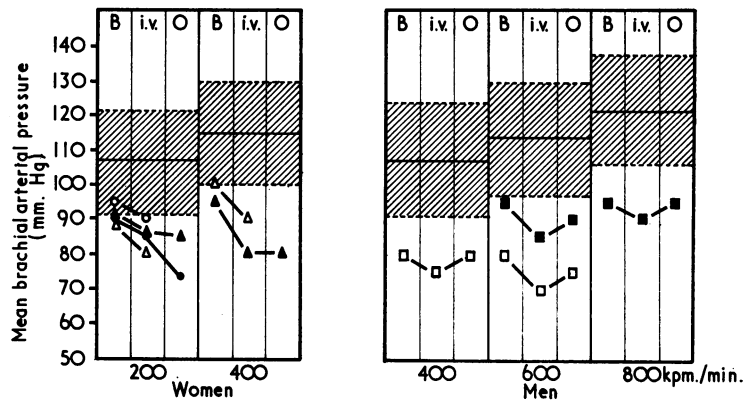

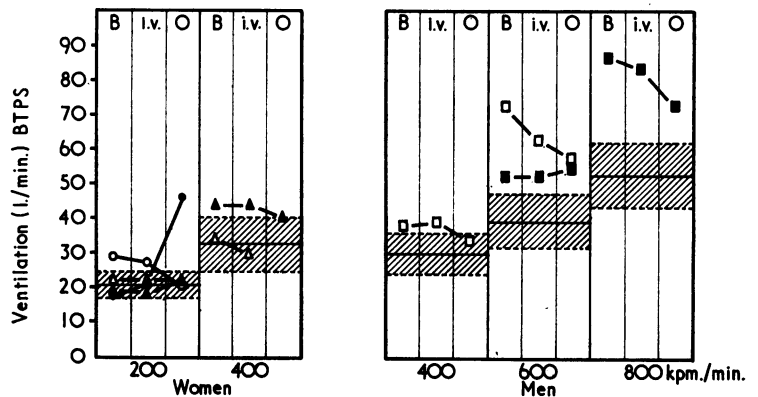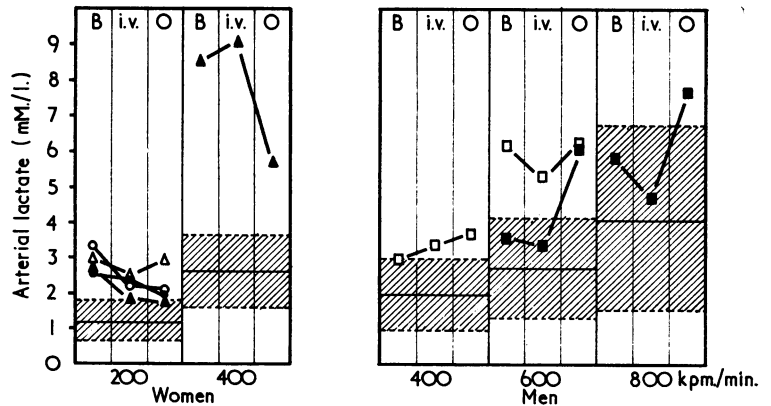FIG. 4 *Changes in brachial arterial mean pressure on exercise. Symbols as in Fig. 1.*

FIG. 5 *Changes in ventilation on exercise. Symbols as in Fig. 1.*

FIG. 6 *Changes in arterial lactate concentration on exercise. Symbols as in Fig. 1.*

Kessel, and Burton, 1967), our findings (Fig. 6) indicate a probable circulatory impairment of oxygen transport to working muscle. A rise in arterial lactate concentration can result in an acidaemia and also in an excessive load of carbon dioxide which has been displaced from tissue bicarbonate and must be excreted by the lungs. These factors tend to stimulate ventilation (Cotes, 1965) and thus can contribute to the symptom of breathlessness. There may also be a reflex stimulation of ventilation from pulmonary vascular receptors, which may explain the high respiratory frequencies found on exercise in our patients (Table 2). From studies in normal subjects (Cumming and Carr, 1966; Eliasch, Rosén, and Scott, 1967; Ulrych *et al.*, 1968) beta-adrenergic blockade would be expected to reduce heart rate and cardiac output with some increase in stroke volume if the effect on cardiac output were less than on heart rate. Cardiac work is reduced, and thus angina, whatever its cause, should be improved (Hamer and Sowton, 1966; Wolfson *et al.*, 1966; Robinson, 1968). Myocardial irritability is reduced so that the occurrence of arrhythmias might be reduced or prevented. Propranolol also prevents the usual increase in left ventricular outflow tract gradient after exercise (Braunwald *et al.*, 1964; Flamm *et al.*, 1968). The increase in ventricular volume resulting from the reduction in heart rate would also be expected to diminish left ventricular outflow tract obstruction (Braunwald *et al.*, 1964; Cherian *et al.*, 1966), though this may be less obvious in the erect than in the supine posture (Mason, Braunwald, and Ross, 1966).

The effect on dyspnoea is less easy to predict in hypertrophic obstructive cardiomyopathy when the symptom is the result of an increase in left ventricular end-diastolic pressure due to resistance to filling of the hypertrophied left ventricle. By diminishing contractility propranolol might increase end-diastolic pressure and thus increase dyspnoea. Acute observations by Flamm *et al.* (1968) and ourselves indicate that left ventricular end-diastolic pressure does not rise after intravenous propranolol though cardiac output may fall by 15 per cent. Dyspnoea was improved in only 16 of 31 patients on long-term oral propranolol treatment (Goodwin, 1970).

Bronchial constriction which may follow propranolol administration occurs in asthmatic but not in normal subjects (Richardson and Sterling, 1969). Spirometry was normal before and after propranolol in our patients making it unlikely that a reduction in ventilatory capacity was contributing to effort dyspnoea.

Since propranolol diminishes cardiac performance, increased fatigue and reduced effort tolerance might be expected in hypertrophic obstructive cardiomyopathy, as has been found in normal subjects (Epstein *et al.*, 1965). Propranolol, however, would be beneficial if excessive and incoordinated contractile function were reduced, angina and obstruction relieved, arrhythmias reduced, and sudden death prevented. Conclusive evidence is lacking on many of these points: angina may be relieved (Flamm *et al.*, 1968) as in Cases 1 and 4 in the present study, but it is not unknown for sudden death to occur during propranolol treatment.

The present study was designed to investigate the effects of propranolol on exercise performance as judged by cardiac output, stroke volume, 'cardiac work', systemic vascular pressures, ventilation, and changes in blood lactate concentration. The results have been predictable in that a reduction in heart rate, blood pressure, and cardiac output occurred while ventilation and blood lactate concentration were largely unchanged. Angina was relieved, probably as a result of a fall in cardiac work. No assessment can be made of the effects on left ventricular diastolic pressures, outflow obstruction, or prognosis. However, a reduction in cardiac work would be valuable in limiting further abnormal hypertrophy; while the bradycardia, and possibly an increased stroke volume might favourably influence the left ventricular outflow tract gradient. Though it has not been possible to show any conspicuous improvement after treatment with propranolol in patients with hypertrophic obstructive cardiomyopathy, we believe that propranolol and other beta-adrenergic blocking agents such as practolol (I.C.I. 50172) (Croxson *et al.*, 1970) have actions that might be beneficial and that further trial of these agents is warranted.

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