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CARDIAC OUTPUT AFTER BETA-ADRENERGIC BLOCKADE IN ISCHÆMIC HEART DISEASE

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The suggestion that blockade of the cardiac sympathetic nerves might be helpful in patients with angina pectoris has received some experimental support (Apthorp, Chamberlain, and Hayward, 1964; Hamer *et al.*, 1964). The increased myocardial contractility during exercise is produced by stimulation of beta-adrenergic sympathetic fibres (Ahlquist, 1948) which are specifically blocked by pronethalol and propranolol (Dornhorst and Robinson, 1962; Black *et al.*, 1964). These drugs have been shown to decrease myocardial contractility under a variety of circumstances, and it seems likely that the consequent reduction in myocardial work might be responsible for their beneficial effect in angina pectoris. In order to assess the mechanisms by which exercise tolerance is increased after beta-adrenergic blockade, we have undertaken a study of the effects of propranolol on cardiovascular function at rest and during exercise in a series of patients with ischæmic heart disease.

Subjects and Methods

In view of the tendency for beta-adrenergic blockade to accentuate any tendency to cardiac failure the study was confined to a selected group of patients with apparently good myocardial function. Patients with extensive or recent infarction or severe angina of effort were excluded, as were those with hypertension, cardiac enlargement, pulmonary congestion, or clinical evidence of left ventricular dysfunction, such as an atrial sound, a third sound, or delayed aortic valve closure.

Eight patients were studied (Table I). Angina of effort was present in 6 and was mild in 3; there had been no change in the severity of this symptom in recent months. Two patients had evidence of minor cardiac infarction in the past with transient S–T segment and T wave changes which had largely regressed at the time of study. The remaining two patients had had moderately severe infarction in the past, with pathological Q waves which had regressed subsequently. The current electrocardiogram was normal in 4 and showed minor changes in the remaining 4.

The patients were studied in the sitting position at rest and during exercise on a Schönander-Elema bicycle ergometer (Holmgren and Mattsson, 1954). The electrocardiogram was followed throughout the study using a modified CR5 lead with the remote electrode on the right shoulder, and was used to measure changes in heart rate.

Cardiac output was measured by the Fick principle. Fine polythene tubing of 1 mm. external diameter (PE 50) was inserted percutaneously into a forearm vein and allowed to drift into the pulmonary artery. The location of the catheter tip was confirmed by pressure measurements using a P23G Statham strain gauge and a Sanborn direct-writer. In some patients similar tubing of slightly larger bore and greater rigidity was inserted percutaneously into the brachial artery. Blood samples were collected from the pulmonary artery and the brachial artery over a two-minute period; approximately 4 ml. of blood was obtained through PE 50 tubing in this time. Oxygen consumption was measured by the collection of expired air over a 5-minute period at rest and from the 4th to the 6th minute of exercise. Four patients were exercised at 100 kpm./min.

TABLE I

CLINICAL FEATURES OF 8 PATIENTS WITH ISCHÆMIC HEART DISEASE

Initials, sex, and age	Angina		Infarction		Casual blood pressure (mm.Hg)	Electrocardiogram at rest
	Present severity (1–4)	Duration (yr.)	Severity	Duration (yr.)		
V.F. F 49	2	6	—	—	165/90	Normal
W.C. M 57	2	1	—	—	110/70	Normal
S.T. M 41	1	2	Minor	2	120/70	Normal
N.L. M 39	1	6	Moderate	6	130/70	Flat T V5 and 6
R.C. M 57	0	—	Moderate	1	130/70	Normal
R.H. M 54	0	—	Minor	1/8	145/80	Tall T in V leads
C.M. M 50	1	6	—	—	150/90	RBBB
T.W. M 56	2	9	—	—	100/70	S–T depression

TABLE II

CHANGES IN CARDIAC OUTPUT AFTER PROPRANOLOL

	Before propranolol			After propranolol		
	Rest	Exercise		Rest	Exercise	
		100 kpm./min.	300 kpm./min.		100 kpm./min.	300 kpm./min.
Number of subjects	8	4	8	8	4	8
P_{AO_2} saturation (%)	68	55	53	*61*	51	*46*
A–V O_2 difference (ml./l.)	62	92	92	77	98	107
O_2 consumption (ml./min.)	295	605	965	280	525	*880*
Cardiac output (l./min.)	5·0	6·9	10·5	*3·8*	5·4	*8·3*
Heart rate (per min.)	80	82	105	71	72	*88*
Stroke volume (ml.)	66	86	104	58	80	97

Statistically significant changes are given in italics.

(16 watts), and all 8 were exercised at 300 kpm./min. (50 watts). After a period of rest of approximately 30 minutes the test was repeated 15 minutes after the intravenous injection of 5 mg. of propranolol (Inderal). Angina pectoris was not produced during this study.

The cardiac output was calculated from the arteriovenous oxygen difference and the oxygen consumption. Blood oxygen content was obtained by the van Slyke method in 4 and from the oxygen tension determined from an Instrumentation Laboratories oxygen electrode in the remaining 4 patients. In 5 an arterial oxygen saturation of 98 per cent was assumed; the remaining 3 showed only minor deviations from this value.

RESULTS

The cardiac output in these patients showed a consistent fall of approximately 22 per cent both at rest and on exercise after propranolol (Table II). There was a significant fall in pulmonary arterial oxygen saturation both at rest ($p < 0.02$) and on exercise ($p < 0.01$), the average change being about 10 per cent. Oxygen consumption also fell by a similar extent, but the changes were significant only on exercise ($p < 0.05$). The fall in cardiac output from 5·0 to 3·8 l./min. at rest and from 10·5 to 8·3 l./min. at 300 kpm./min. (50 watts) was significant in both situations ($p < 0.02$). A consistent reduction in heart rate of approximately 13 per cent was observed, but the changes were significant only on exercise ($p < 0.01$). The consequent slight reduction in stroke volume was not statistically significant. There was no consistent change in pulmonary or systemic arterial pressure after propranolol. The cardiac output changes in each subject are shown in Table III.

TABLE III

CARDIAC OUTPUT AT REST, AND AT TWO WORK LOADS IN 8 PATIENTS* WITH ANGINA PECTORIS BEFORE AND AFTER PROPRANOLOL

	Cardiac output (l./min.)						Method
	Before propranolol			After propranolol			
Work load (kpm./min.)	Rest	100	300	Rest	100	300	
Initials							
V.F.	4·9		13·7	3·5		10·3	Po_2†
W.C.	7·5	8·1	11·1	4·6	6·0	9·1	Po_2
S.C.	6·1	8·0	12·4	4·5	5·7	8·4	vS
N.L.	4·9		9·5	3·7		6·6	vS†
R.C.	2·8	5·2	7·4	2·8	4·2	6·8	vS†
R.H.	3·6	5·7	9·0	3·3	5·7	7·7	vS†
C.M.	5·0		11·0	4·0		9·5	Po_2†
T.W.	5·5		11·2	4·1		8·2	Po_2

Po_2 = oxygen electrode; vS = van Slyke.
* Only 4 subjects studied at 100 kpm./min.
† Arterial oxygen saturation assumed.

DISCUSSION

The demonstration of a reduction in cardiac output both at rest and during exercise after beta-adrenergic blockade provides clear evidence of a change in cardiac work which might be expected to benefit a patient with angina pectoris. Similar changes have recently been reported in normal subjects (Robinson *et al.*, 1965). However, the improved utilization of the limited myocardial oxygen supply from a reduced force of contraction may also play a part in improving exercise tolerance in patients with coronary artery disease (Apthorp *et al.*, 1964).

Studies with the earlier analogue pronethalol have shown little change in cardiac output from beta-adrenergic blockade. However, Chamberlain and Howard (1964) showed a tendency to a low output after the drug, using earpiece dye curves in normal subjects on exercise, and Bishop and Segel (1963) found a fall in output under most circumstances at rest and on exercise in normal subjects. The possibility of a difference in effect between pronethalol and propranolol must be considered.

The reduction in oxygen consumption after propranolol in these patients and in the normal subjects of Robinson *et al.* (1965) may indicate reduced myocardial oxygen consumption due to the reduction in cardiac work. Alternatively, reduced contractility of skeletal muscle from beta-adrenergic blockade may be responsible. The ability to maintain exercise at a moderate work load with a lower cardiac output indicates an improved efficiency of the organism in the strict sense. However, the improvement is gained at the expense of considerable reduction in blood flow, at least in some parts of the peripheral vascular bed.

Although bradycardia is a striking feature of the response to beta-adrenergic blockade, the changes in cardiac output in the present study appeared to outweigh the effects of reduced heart rate, so that there is a tendency to a reduction in stroke volume both at rest and on exericse. In normal subjects Bishop and Segel (1963) found an increase in stroke volume during upright exercise after pronethalol, while Robinson *et al.* (1965) using propranolol found no change. It seems likely that the fall in cardiac output after beta-adrenergic blockade is greater in patients with ischæmic heart disease than in normal subjects.

One function of the cardiac sympathetic system is to facilitate ventricular filling by increasing myocardial diastolic compliance (Whalen *et al.*, 1963; Mitchell, Linden, and Sarnoff, 1960), and interference with this mechanism may reduce the stroke volume at rapid heart rates; however, these changes are unlikely to be responsible for the reduction in cardiac output at rest and at moderate work loads reported here.

SUMMARY

A reduction in cardiac output of approximately 22 per cent was demonstrated at rest and on exercise in 8 patients with ischæmic heart disease after beta-adrenergic blockade with propranolol.

The changes are attributed to a reduction in myocardial contractility in association with a fall in heart rate. The lower cardiac output is one factor tending to reduce myocardial work and to improve exercise tolerance in angina pectoris after propranolol.

Any improvement in myocardial oxygenation after beta-adrenergic blockade is attained at the expense of an impairment of myocardial contractility and a fall in peripheral blood flow.

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