Haemodynamic Effects of Beta-adrenergic Blockade

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Several studies have shown a beneficial effect in treating patients with coronary disease with beta-adrenergic blockade (Hamer and Sowton, 1965; Grant *et al.*, 1966; Gillam and Prichard, 1966; Rabkin *et al.*, 1966). In normal subjects blockade with propranolol decreases cardiac output both at rest and during exercise mainly by reducing heart rate, and increases the end-diastolic pressure in the left ventricle, which would suggest some deterioration of left ventricular function (Cumming and Carr, 1966). In subjects with hyperkinetic circulation the effect of blockade is more pronounced (Bollinger, Gander, and Forster, 1965).

Malmberg (1965) found that patients with coronary disease had a hypokinetic circulation compared with controls of about the same age, and more than 50 per cent of these patients had increased left ventricular filling pressure during exercise. Hamer and Sowton (1965) predicted a greater fall in cardiac output after beta-adrenergic blockade in patients with ischaemic heart disease than in normal subjects. The purpose of the present investigation was to study the influence on the circulation of beta-adrenergic blockade during exercise which induced angina pectoris.

SUBJECTS AND METHODS

There were 5 normal people (age 19–23 years) and 8 patients with coronary heart disease (age 38–56 years). Some anthropometric data are listed in Table I. The normal subjects were all in hospital for investigation by heart catheterization because of an early systolic ejection murmur in the pulmonary area which could be physiological or caused by a small atrial septal defect. The investigation excluded a shunt and the circulation was found to be normal.

All patients had a history of typical effort angina which limited their working capacity. One patient (Case 6)

had an infarction one year before the investigation, but none had clinical signs of heart failure or any other disease of importance. One patient (Case 4) had been operated on by the Vineberg method one year earlier, without clinical success.

Angiography of the coronary vessels was performed in all patients and showed moderate to marked atheromatous changes in the main branches, except in one patient, who had changes of a peripheral type (Case 7) (Nordenström, 1964). The electrocardiogram was normal at rest in 6 patients (Cases 1–4 and 7–8) but showed abnormal changes during and after exercise in all patients.

Exercise tolerance tests were performed on a bicycle ergometer (Holmgren and Mattsson, 1954) in sitting and supine positions with stepwise increase of the work load by 200 or 300 kpm/min., depending on the severity of symptoms. The methods for heart catheterization were the same as described earlier from this laboratory (Bevegård, Holmgren, and Jonsson, 1960). The aortic pressure was obtained with a catheter*, introduced percutaneously into the brachial artery and placed in the aortic arch. The reference level for zero pressure was taken as the mid-thoracic point. The cardiac output was determined according to the direct Fick principle.

The duration of mechanical diastole was measured from the incisura of the central aortic pressure curve to the start of the uprise of the next stroke. Left ventricular external work was calculated as the product of cardiac output and the mean aortic pressure.

pH, carbon dioxide, and standard bicarbonate were determined with the micro-equilibration technique (Astrup, 1956).

All patients were investigated in the morning, first at rest and then at a work load (range 200–600 kpm/min.) which caused moderate anginal pain and which all patients could continue for about 6–8 minutes. Expired air was collected and blood samples were withdrawn between the 4th and the 6th minute of exercise. After a resting period of 30–45 minutes the study was repeated in exactly the same way 15 minutes after intravenous injection of 5–10 mg. propranolol. None of the patients complained of any praecordial symptoms when performing the same load after propranolol.

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* Teflon catheter.

TABLE I
SOME ANTHROPOMETRIC AND FUNCTIONAL DATA IN 8 PATIENTS WITH ANGINA PECTORIS AND 5 HEALTHY SUBJECTS

Case No., sex, and age			Height (cm.)	Weight (kg.)	Body surface area (m. ²)	Total Hb (g.)	Blood volume (l.)	Heart volume, supine (ml.)	Exercise tolerance test in sitting position		
									kpm/min.	Duration (min.)	Heart rate (beats/min.)
<i>Patients with Angina Pectoris</i>											
1	M	53	177	68	1.86	750	4.6	825	400	2	132
2	M	51	176	79	1.95	690	4.8	910	400	2	106
3	M	56	171	86	1.97	925	5.7	840	900	2	140
4	M	41	157	57	1.57	445	3.5	—	400	4	175
5	M	54	174	65	1.80	525	4.0	710	600	6	148
6	M	56	178	85	2.04	1035	6.3	1250	600	6	150
7	F	48	173	80	1.94	550	4.2	700	400	6	142
8	M	38	166	74	1.82	675	4.7	900	900	2	156
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<i>Healthy Subjects</i>									W ₁₇₀ (kpm/min.)*		
9	M	23	167	72	1.81	760	4.7	—	1025		
10	F	23	165	66	1.73	550	4.1	700	550		
11	M	22	181	65	1.86	705	4.6	850	1125		
12	F	22	163	52	1.56	420	3.2	500	425		
13	M	19	179	68	1.88	700	4.5	660	750		

* $\dot{W}_{170}$ = rate of work at a heart rate of 170 beats/min.

RESULTS

Mean values of some haemodynamic and respiratory variables are given in Table II. The findings after beta-receptor blockade are expressed as percentages of the measurements during the control period.

(a) *Healthy Subjects.* Oxygen consumption decreased by 11 per cent ($p < 0.05$) at rest. During exercise there was a small but not significant fall and thus an almost unchanged mechanical efficiency after blockade. Cardiac output decreased by 29 per cent ($p < 0.05$) at rest and by 20 per cent ($p < 0.01$) during work. The reduction at rest was dependent on a slowing of the heart rate by 16 per cent ($p < 0.02$) as well as a reduction of the stroke volume by 13 per cent ($p < 0.05$). During exercise, however, the stroke volume did not change significantly and the change in cardiac output was a result of a lower heart rate only. There was no change in pulmonary arterial wedge or aortic mean pressure at rest, but during exercise the wedge pressure increased by 40 per cent (15 to 21 mm.Hg, $p < 0.001$) and the right ventricular end-diastolic pressure by 55 per cent (7 to 11 mm. Hg), but the systemic arterial pressure did not change significantly. The acid-base balance and the respiratory quotient were unchanged at rest and during work after propranolol.

(b) *Patients with Coronary Heart Disease.* Oxygen consumption was reduced both at rest and during exercise ($p < 0.01$) and thus mechanical efficiency was increased, though by rather a small

amount (from 22 to 23%). The cardiac output at rest diminished by 26 per cent (from 6.8 to 5.0 l./min., $p < 0.02$), and during work by 17 per cent (from 10.9 to 9.1 l./min., $p < 0.01$). This change was due to a decrease of both stroke volume (16%) and heart rate (10%) at rest, but during exercise it was only the result of a fall in heart rate (17%) (Fig. 1).

The mean pressure in the aorta did not change significantly at rest or during work, which means that the peripheral vascular resistance increased after propranolol. Left ventricular work thus decreased in proportion to the smaller cardiac output. The fall amounted to 26 per cent at rest and 20 per cent ($p < 0.02$) during work (Fig. 2).

The ventricular filling pressures during work, though high during the control period, did not change significantly after blockade (there was a slight decrease in wedge pressure from 32 to 27 mm.Hg and a small increase in the right ventricular end-diastolic pressure from 12 to 15 mm.Hg).

There was no difference in pH or standard bicarbonate after beta-adrenergic blockade (Table II), and a slight decrease in respiratory quotient.

The negative chronotropic effect of propranolol prolongs the duration of the mechanical diastole in relation to a slower heart rate in a normal way (Fig. 3). Thus the systolic ejection time measured on the central aortic pressure curve is not increased.

DISCUSSION

Several haemodynamic studies dealing with beta-adrenergic blockade have been reported. *Proneth-*

TABLE II

MEAN VALUES FOR HAEMODYNAMIC VARIABLES BEFORE AND AFTER PROPRANOLOL INJECTION, FOR INDIVIDUAL DIFFERENCES, AND SIGNIFICANCE OF DIFFERENCES IN 8 PATIENTS WITH EFFORT ANGINA AND 5 HEALTHY SUBJECTS

		O ₂ uptake (ml./min.)	Arterio- venous O ₂ diff. (ml./l.)	Cardiac output (l./min.)	Heart rate (beats/ min.)	Stroke volume (ml.)	Pressure (mm.Hg)				Left vent. work (kpm/min.)	pH	Standard bicar- bonate (mEq/l.)
							Aorta (mean)	Pulm. art. wedge (mean)	Pulm. art. (mean)	Rt. vent. end- diastolic			
<i>Patients with Angina Pectoris</i>													
<i>(a) Rest</i>													
Before propranolol	272	42.0	6.8	79	85	104	9	16	7	9.9	7.45	25.0	
After propranolol	253	51.4	5.0	71	72	103	10	17	7	7.4	7.45	23.9	
Number	8	8	8	8	8	8	8	8	7	8	4	4	
Mean for individual differences	19	-9.4	1.8	8	13	1	-1	-1	—	2.5	—	1.1	
Probability	<0.01	<0.01	<0.02	<0.02	<0.02	>0.8	>0.5	>0.3	—	>0.05	—	—	
<i>(b) Exercise</i>													
Before propranolol	1148	107.0	10.9	128	87	130	32	40	12	19.6	7.38	21.3	
After propranolol	1086	118.9	9.1	107	85	127	27	38	15	15.6	7.38	22.0	
Number	8	8	8	8	8	8	8	8	7	8	4	4	
Mean for individual differences	62	-11.9	1.8	21	2	3	5	2	-3	4.0	—	0.7	
Probability	<0.01	<0.05	<0.01	<0.01	>0.7	>0.3	>0.1	>0.5	>0.1	<0.02	—	—	
<i>Healthy Subjects</i>													
<i>(a) Rest</i>													
Before propranolol	292	35.8	8.8	84	106	91	11	15	7	11.7	7.43	24.3	
After propranolol	260	42.6	6.2	70	92	91	11	14	7	8.2	7.42	23.3	
Number	5	5	5	5	5	5	5	5	5	5	3	3	
Mean for individual differences	32	-6.8	2.6	14	14	—	—	1	—	3.5	0.01	1.0	
Probability	<0.05	<0.05	<0.05	<0.02	<0.05	—	—	>0.2	—	>0.05	—	—	
<i>(b) Exercise</i>													
Before propranolol	1678	99.2	16.9	150	113	117	15	24	7	28.4	7.36	19.7	
After propranolol	1620	119.0	13.5	125	109	111	21	29	11	21.3	7.34	19.7	
Number	5	5	5	5	5	5	5	5	5	5	3	3	
Mean for individual differences	59	-19.8	3.4	25	4	6	-6	-5	-4	7.1	0.02	—	
Probability	>0.4	<0.02	<0.01	<0.001	>0.5	>0.1	<0.001	<0.01	<0.05	<0.05	—	—	

Angina pectoris

n=8 Age 38-56

I Before propranolol

II After

○ Rest

● Work

FIG. 1.—Cardiac output, stroke volume, and heart rate before ($\dot{Q}_I$, SV_I , and HR_I) and after ($\dot{Q}_{II}$, SV_{II} , and HR_{II}) propranolol in 8 patients with coronary heart disease at rest and during exercise. Square with circle represents mean value.

FIG. 2.—Left ventricular external work, mean aortic pressure, and mean pulmonary arterial wedge pressure before ($W_{LV I}$, $\bar{P}_{Ao I}$, and $\bar{P}_{PCV I}$) and after ($W_{LV II}$, $\bar{P}_{Ao II}$, and $\bar{P}_{PCV II}$) propranolol in 8 patients with coronary heart disease.

FIG. 3.—Duration of the mechanical diastole (csec.) in relation to heart rate (beats/min.) in 8 patients with coronary heart disease before and after propranolol. Regression line for healthy subjects.

alol had a significant effect on heart rate (Bishop and Segel, 1963; Schröder and Werkö, 1965) but no change in stroke volume was noted at rest, and during exercise it even increased (Dornhorst and Robinson, 1962; Schröder and Werkö, 1965; Segel and Bishop, 1965; Chamberlain and Howard, 1964), so that cardiac output remained on the whole rather constant, as did the systemic and pulmonary arterial pressure. The later blocking substance, propranolol, is stronger than pronethalol and the difference in effect between these two must be considered (Hamer and Sowton, 1965) when beta-adrenergic blockade in general is discussed (McInerney, Gilmour, and Blinks, 1965).

The finding in this study that the cardiac output reduction after *propranolol* at rest is the result of both a decrease in heart rate and stroke volume is in agreement with other observations (Hamer and Sowton, 1965). This fall in stroke volume is probably due to the negative inotropic effect of propranolol with diminished myocardial contractility. Part of these changes could be due to impaired filling from the venous side as there also is a blocking effect on venous vessels (Kaiser, Ross, and Braunwald, 1964) that could give increased peripheral pooling of blood. However there is no change in the end-diastolic pressure of the right ventricle. Robinson *et al.* (1965) found no change in stroke volume at rest.

During work, however, propranolol did not produce any change in stroke volume and the reduction in cardiac output was, therefore, caused by the lower heart rate only. Since the systemic arterial pressure is unchanged after blockade, the left ventricular work also decreases in proportion to the decrease in heart rate. Although a normal stroke volume is maintained in healthy subjects, the higher filling pressures in both ventricles indicate the importance of sympathetic action on the myocardium during work (Mitchell, Linden, and Sarnoff, 1960). In patients with coronary heart disease the hypokinetic circulation during work after blockade is also due to the relative bradycardia. All patients could maintain an unchanged stroke volume during work, though with a high filling pressure, which has a slight tendency to decrease after blockade. Whether this is due to a more adequate oxygen supply to the myocardium, to the performance of a smaller amount of work, or to the fact that the circulatory system in these patients has not been loaded to the same degree, because of limiting angina, cannot be stated. Hamer and Sowton (1965) predicted a greater fall in cardiac output after beta-adrenergic blockade in patients with ischaemic heart disease than in normal subjects. This is contrary to the present result where the more "hyperkinetic" normal subjects had a more marked

reduction in cardiac output both at rest and during work compared to the "hypokinetic" patients, who reacted with a smaller change in output after blockade.

During exercise about the same amount of oxygen is delivered to the periphery by a smaller cardiac output after blockade and thus the peripheral oxygen extraction is increased, but the skeletal muscle is working with the same relation between aerobic and anaerobic metabolism, as no metabolic acidosis occurs after blockade. Probably other organs besides the working muscle are deprived of blood flow, and this may be of importance in cases where blood flow is restricted by disease. Propranolol blocks the catecholamine-induced increase of free fatty acids (Harrison and Griffin, 1965), but according to the present study it does not seem to interfere with the energy-delivering metabolism during work of short duration, as the respiratory quotient increases to the same amount before and after beta-adrenergic blockade.

SUMMARY

Studies were made on 5 healthy subjects and 8 patients with coronary heart disease, verified by coronary angiography, at rest and during exercise which induced angina pectoris, before and after beta-adrenergic blockade.

The relief of pain during work after blockade in all patients could be explained by a significant decrease in left ventricular work of 20 per cent. This decrease was related to the fall in heart rate, as stroke volume and systemic arterial pressure were unchanged. The abnormally high filling pressures for the ventricles during work decreased slightly after blockade. This was contrary to the findings in healthy subjects who had a reduction of left ventricular work by 25 per cent but an increase in the diastolic filling pressures during submaximal exercise after blockade.

No changes were found in the acid-base balance or the respiratory quotient that would indicate any metabolic disturbances during work of short duration.

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