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Haemodynamic effects of practolol

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The acute haemodynamic effects of administration of 5 mg and 20 mg practolol were studied at cardiac catheterization. In 6 patients with mitral valve disease and atrial fibrillation, there was a dose-related reduction in ventricular rate, with a corresponding increase in stroke volume, while cardiac output, pulmonary arterial, aortic, and left ventricular end-diastolic pressures were unaltered. In 10 patients with aortic regurgitation, in sinus rhythm, a similar reduction in heart rate was also accompanied by an increase in stroke volume, though after the higher dose there was a small reduction in cardiac output. These changes were accompanied by significant reductions in left ventricular dP/dt, left ventricular Vmax, and after the higher dose, in left ventricular end-diastolic pressure. These results confirm that the depressant effect of practolol on cardiac output is small, and show that, under the conditions of the study, stroke volume was not limited by left ventricular contractile state or filling pressure. It is suggested, therefore, that cardiac output was determined by the peripheral circulation rather than directly by ventricular performance, and that the haemodynamic effects of practolol differed from those of other beta-adrenergic blocking drugs since significant peripheral circulatory beta sympathetic activity was preserved.

The cardioselective beta-adrenergic blocking drug, practolol, has proved effective in the management of a variety of supraventricular and ventricular arrhythmias in patients with severe heart disease (Gibson, Balcon, and Sowton, 1968; Jewitt, Mercer, and Shillingford, 1969). Its use in this situation is justified by studies which show it to cause less depression in cardiac output than propranolol when doses leading to an equal reduction in heart rate are compared (Gibson and Sowton, 1968; Sowton *et al.*, 1968; Jewitt, Burgess, and Shillingford, 1970; Finegan, Marlon, and Harrison, 1970). It has been suggested that the difference in effect of cardiac output might reflect the relative actions of the two drugs on the force of left ventricular contraction. The present study was undertaken to examine the relation between left ventricular contractile state, left ventricular filling pressure, and cardiac output after practolol administration in patients with heart disease. The results show that an increase in stroke volume may occur despite depression of left ventricular contractile state and no change, or a reduction, in left ventricular filling pressure. The findings are not, therefore, compatible with the suggestion that the force of left ventricular contraction is the factor limiting stroke volume under the conditions of the study. The explanation of the difference in action of the two drugs on cardiac output must therefore be sought elsewhere in the circulation.

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Material and methods

Sixteen patients, in whom practolol treatment might be needed later to control atrial fibrillation or postoperative arrhythmias, were studied during diagnostic cardiac catheterization. Six patients had either mitral stenosis or mixed mitral valve disease and atrial fibrillation (Group I). Patients with very high pulmonary vascular resistance (greater than 10 units) or those with conspicuous left atrial enlargement were not studied. Ten patients had aortic regurgitation and were in sinus rhythm (Group II); none had a significant systolic pressure gradient across the aortic valve, nor was mitral regurgitation shown at subsequent angiography. Clinical and haemodynamic details of the patients are given in Table 1. The patients were studied after an overnight fast and without premedication. All were on maintenance digoxin and diuretic therapy which was not interrupted for the study. The nature and purpose of the investigation were explained to them and their consent obtained.

Pulmonary arterial pressures were measured with a No. 7 Cournand catheter, and left ventricular and aortic pressures with a No. 7 or No. 8 N.I.H. catheter, using Statham P23Gb strain gauge transducers and a Sanborn photographic

TABLE I *Clinical details*

Mitral valve disease – Group I

Case No.	*Age*	*Sex*	*Body surface area (m^2)*	*Mean pulmonary arterial pressure (mmHg)*	*Pulmonary vascular resistance (units)*	*End-diastolic mitral valve gradient (mmHg)*	*Diagnosis*
1	46	M	1·9	24	2·5	2	Trivial mitral stenosis; large left ventricle
2	57	M	1·7	23	4·5	0	Mitral regurgitation grade 2/4
3	49	F	1·5	15	1·5	4	Mitral regurgitation grade 2/4
4	56	F	1·4	12	1·5	8	Trivial mitral regurgitation (1/4)
5	59	F	1·5	17	2·5	8	Mitral regurgitation 1/4
6	52	F	1·6	32	5·0	15	No mitral regurgitation

Aortic valve disease – Group II

Case No.	*Age*	*Sex*	*Body surface area (m^2)*	*Mean pulmonary arterial pressure (mmHg)*	*Left ventricular end-diastolic pressure (mmHg)*	*? Bacterial endocarditis*	*Other conditions*
1	43	F	1·6	30	20	—	Mitral stenosis (confirmed by ultrasound)
2	56	F	1·8	15	20	—	Aneurysmal ascending aorta
3	48	M	1·9	47	22	Yes	—
4	50	M	1·9	22	5	—	Mitral stenosis (confirmed by ultrasound)
5	40	M	2·0	22	35	Yes	—
6	57	M	1·9	18	17	—	Cardiomyopathy
7	55	M	1·8	10	6	—	Cardiomyopathy
8	54	F	1·6	15	0	—	—
9	24	M	2·1	10	2	Yes	—
10	17	M	1·9	30	8	—	—

recorder operating at paper speeds of 25 and 50 mm/sec. The zero for pressure measurement was taken as the sternal angle and mean pressures were derived by electrical integration. In three patients with aortic regurgitation, left ventricular pressures were measured through the fluid-filled lumen of an SF1 catheter. In all patients left ventricular end-diastolic pressure was taken as the mean of ten successive beats, and in patients in sinus rhythm was measured immediately after the 'a' wave. Cardiac output was measured by the indicator dilution technique. A bolus of 10 mg indocyanine green was injected into the pulmonary artery and arterial blood was withdrawn from the aortic root by a constant-rate syringe through a Gilford cuvette densitometer feeding a wide-chart recorder. After each determination blood was returned to the patient. Calibration was by the dynamic method using 20 μl of dye (Shinebourne, Fleming, and Hamer, 1967). All cardiac output determinations were made in duplicate and over the study the root mean square of the difference between duplicate determinations was 0·26 l./min. Heart rate was measured from an electrocardiogram recorded during the inscription of the dye curves and in patients with atrial fibrillation was averaged over 40 successive beats. Oxygen saturations of blood samples withdrawn from aorta and pulmonary artery were estimated using a Kipp Haemoreflector. The rate of rise of left ventricular pressure was measured with a catheter tip manometer (SF1) in 3 patients and a fluid-filled catheter (7 or 8 N.I.H.) in 5, the results being similar using the two methods. The signal from the transducer was processed by a differentiating amplifier whose frequency response was similar to that described by Knopp, Rahimtoola, and Swan (1970).

The velocity of contraction of the contractile elements (V_{CE}) was determined by the method of Mason, Spann, and Zelis (1970) as Vmax, using a value of 32 per muscle length for K, the coefficient of series elasticity. Stroke volume was taken as cardiac output divided by heart rate and oxygen uptake as the product of cardiac output and arteriovenous oxygen difference.

The present investigation was performed after diagnostic pressures had been measured, but before angiography. Doses of 5 mg and 15 mg (i.e. a total dose of 20 mg) practolol, as hydrochloride, were given into the pulmonary artery. Measurements were made in the control state and 5 minutes after each injection. Statistical analysis was by Student's 't' test for paired comparisons.

There was no significant side effect of the investigation.

Results

Heart rate Practolol caused a dose-related reduction in ventricular rate in both groups of patients. In those with mitral valve disease, who were in atrial fibrillation, it was 8·5 beats/min after the lower dose, and 13 beats/min after the higher, while in the patients with aortic regurgitation who were in sinus rhythm, the corresponding changes were 8·3 and 14 beats/min, all with respect to control values ($P < 0.01$ for all changes).

Pressures Mean aortic and pulmonary arterial pressures did not change significantly after practolol administration. Left ventricular end-diastolic pressure was high in the patients with aortic regurgitation, but was significantly reduced by 4 mmHg after the higher dose of practolol ($P < 0.05$). Mean left ventricular end-diastolic pressure was normal in the patients with mitral valve disease, and was unaffected by practolol.

Blood flow In the patients with aortic regurgitation, the mean resting cardiac output was 4·1 l./min. This was unaltered by 5 mg practolol, but was significantly reduced after 20 mg by 0·23 l./min ($P < 0.05$). In the patients with mitral valve disease, the resting cardiac output was 3·3 l./min, and was unaffected by either dose. The reduction in heart rate, however, resulted in a significant increase in stroke volume in both groups of patients; by 3·5 ($P < 0.05$) and 8 ml ($P < 0.01$) after the two doses of practolol in those with mitral valve disease, and by 3·2 ml ($P < 0.01$) and 5 ml ($P < 0.01$) in those with aortic regurgitation.

Left ventricular function This was assessed only in the patients with aortic regurgitation, in whom disease of the left ventricle was suggested by low control values of both peak dP/dt (mean 1580 mmHg/sec) and Vmax (mean 0·75 muscle lengths/sec). In two patients, Vmax could not be measured, since peak values of V_{CE} had not occurred before the aortic valve opened. There was a mean reduction in left ventricular peak dP/dt by 280 mmHg/sec ($P < 0.01$) after administration of 5 mg practolol and by 430 mmHg/sec after 20 mg ($P < 0.01$). The corresponding changes in Vmax were 0·07 ($P < 0.05$) and 0·084 muscle lengths/sec ($P < 0.05$).

TABLE 2 *Results*

Group I

n = 6	*Control*	*Change after*	
		5 mg	*20 mg*
Heart rate (beats/min)	77 ± 3·7	−8·5 ± 3·1†	−13 ± 4·0†
Cardiac output (l./min)	3·3 ± 0·56	−0·2 ± 0·2	−0·15 ± 0·2
Mean aortic pressure (mmHg)	94 ± 10·1	−0·1 ± 3·3	−5 ± 5·0
Mean pulmonary arterial pressure (mmHg)	20 ± 7·8	−0·5 ± 2·7	−2 ± 2·4
Left ventricular end-diastolic pressure (mmHg)	6 ± 2·2	−1 ± 3·4	−2 ± 2·3
AV O_2 difference (ml/l.)	62 ± 8·2	+4 ± 5·2	+7 ± 8·1
Stroke volume (ml)	44 ± 12·4	+3·5 ± 3·0*	+8 ± 3·5†
O_2 uptake (ml/min)	205 ± 48	0	+7 ± 28

Group II

n = 10	*Control*	*Change after*	
		5 mg	*20 mg*
Heart rate (beats/min)	81 ± 1·8	−8·3 ± 5·8†	−14 ± 9·3†
Cardiac output (l./min)	4·1 ± 0·03	−0·1 ± 0·22	−0·32 ± 0·42*
Mean aortic pressure (mmHg)	93 ± 18	−0·5 ± 9·0	−2 ± 12
Mean pulmonary arterial pressure (mmHg)	18 ± 7·1	−1·5 ± 3·5	−1·4 ± 4·7
Left ventricular end-diastolic pressure (mmHg)	14·0 ± 9·5	−3·0 ± 5·3	−4·0 ± 5·0*
AV O_2 difference (ml/l.)	51 ± 12·8	−0·4 ± 3·0	+6·7 ± 5·5†
Left ventricular peak dp/dt (mmHg/sec) (n = 8)	1580 ± 340	−280 ± 150†	−430 ± 190†
Stroke volume (ml)	48 ± 12	+3·2 ± 2·4†	+5·5 ± 4·5†
O_2 uptake (ml/min)	225 ± 34	−15 ± 22	+28 ± 24†
Vmax (muscle lengths/sec) (n = 6)	0·75 ± 0·22	−0·070 ± 0·045*	−0·084 ± 0·055†

Mean values ± 1 standard deviation.
* $P < 0.05$.
† $P < 0.01$.

Oxygen uptake The only significant change in oxygen uptake was a small increase of 28 ml/min ($P < 0.01$) after the higher dose of practolol in the patients with aortic regurgitation. This was associated with an increase in arteriovenous oxygen difference of 6·7 ml/l. ($P < 0.01$).

The results are given in detail in Table 2.

Discussion

The present results confirm previous findings that practolol causes dose-related reduction in heart rate in patients with sinus rhythm or atrial fibrillation. This was associated with a small reduction in cardiac output only in patients with aortic regurgitation and, therefore, with an increase in stroke volume in both groups of patients similar to that previously described in normal subjects (Gibson and Sowton, 1968) and patients with ischaemic heart disease (Sowton *et al.*, 1968; Jewitt *et al.*, 1970). There was no associated change in mean aortic pressure, but a significant reduction in left ventricular end-diastolic pressure in the patients with aortic regurgitation after the higher dose. Reduction in left ventricular end-diastolic pressure has also been observed by Wolfson and Gorlin (1969) after propranolol administration in patients with ischaemic heart disease, by Bensaid, Scebat, and Lenègre (1970) after oxprenolol in patients with rheumatic heart disease, and by Webb-Peploe *et al.* (1971) after practolol in patients with hypertrophic cardiomyopathy.

Practolol also caused a reduction in the maximum rate of rise of left ventricular pressure, previously reported by Finegan *et al.* (1970) on exercise. Since this quantity may be affected by changes in left ventricular end-diastolic pressure or in aortic end-diastolic pressure, a reduction in peak dp/dt cannot necessarily be taken as evidence of a change in left ventricular contractile state. Though there is disagreement over methods of assessing ventricular contractility (Pollack, 1970), Mason *et al.* (1970) have shown that dp/dt divided by instantaneous developed pressure and extrapolated to zero pressure provides a measure that reflects the action of known positive inotropic stimuli which is independent of preload and afterload. The consistent reduction in this quantity (Vmax) in the present study therefore suggests that practolol had a negative inotropic effect in the patients studied. It is possible that this was due directly to a reduction in heart rate, though the effects of such changes induced by right atrial pacing in man are small (Sonnenblick *et al.*, 1965), but it seems more likely to be due to competitive inhibition of the positive inotropic effect of sympathetic stimulation or circulating catecholamines. This is in line with experimental evidence in the anaesthetized dog, where inhibition of the positive inotropic effects of catecholamines occurs at similar dose levels to those blocking the increase in heart rate (Dunlop and Shanks, 1968).

It has been suggested that the different haemodynamic actions of practolol and propranolol are due to differences in their effects on the force of left ventricular contraction, due either to the partial agonist activity of practolol or the direct myocardial depressant effect of propranolol (Jewitt *et al.*, 1970). The partial agonist activity of practolol is unlikely to be responsible since alprenolol and oxprenolol, which both have this property, cause a dose-related reduction in cardiac output similar to propranolol, with no significant increase in stroke volume (Gibson, 1971). The differences are also unlikely to be due to the direct myocardial depressant effects of propranolol since these effects are manifest *in vitro* only at concentrations several orders of magnitude higher than therapeutic blood levels (Coltart and Meldrum, 1970; Coltart, Gibson, and Shand, 1971). Furthermore, the present results show that, in the patients studied, the force of left ventricular contraction could not have been the limiting factor, since stroke output rose after practolol in spite of a consistent depression of left ventricular contractile state. The associated failure of left ventricular end-diastolic pressure to rise in either group, with a significant fall in the patients with aortic regurgitation, suggests that, under the conditions of the experiment cardiac output was not limited by either of the recognized determinants of myocardial function but by a reduction in venous return produced by changes in the peripheral vascular bed (Guyton, 1968). Differences between practolol and the other beta blocking drugs are therefore likely to be due to its cardio-selectivity, implying the presence of significant adrenergic peripheral vasodilator activity under the conditions of the study. Evidence for blockade of such activity by low doses of alprenolol and sotalol during exercise in normal subjects has previously been presented (Gibson, 1971); the present group of patients with severe heart disease might be expected to show a similar effect at rest. Even if such activity were absent in the control state, haemodynamic changes caused by cardiac beta-adrenergic blockade might themselves evoke a reflex increase in peripheral adrenergic tone, which would be in-

hibited by a non-selective beta blocking drug, but be little affected by practolol in the doses used. The increase in oxygen uptake associated with the higher dose of practolol may have a similar basis. The clinical significance of peripheral beta stimulation has also been shown by the increase in cardiac output caused by intravenous administration of salbutamol in the absence of positive inotropic effect on the left ventricle (Gibson and Coltart, 1971). These conclusions do not necessarily apply to patients with severe heart failure or cardiogenic shock, in whom heart rate or force of left ventricular contraction may limit cardiac output, and cardiac as well as peripheral actions contribute to the overall effect of beta-adrenergic blocking drugs on the circulation.

Since the differences between practolol and other beta-adrenergic blocking drugs on cardiac output cannot be directly ascribed to effects on the force of left ventricular contraction, it is probable that other non-selective drugs, even with partial agonist activity or lacking direct myocardial depressant action, will have effects on cardiac output similar to those of propranolol. The advantage of practolol appears to lie in its cardioselectivity which is responsible for its lack of effect on the peripheral circulation as well as its reduced liability to cause an increase in airways resistance in asthmatic subjects (Macdonald and McNeill, 1970).

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