

Effect of atenolol (ICI 66 082) on coronary haemodynamics in man

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The coronary haemodynamic effect of atenolol, a new cardioselective beta-adrenergic blocker, was studied in 15 patients with angina pectoris.

Myocardial blood flow from the anterolateral part of the left ventricle was measured by the continuous infusion thermodilution method by means of a two-thermistor catheter with pacing electrodes placed in the great cardiac vein. Catheters were also positioned in the pulmonary artery and the thoracic aorta for blood sampling, pressure measurements, and cardiac output determination. Investigations were performed at rest, at slow, and at submaximal atrial pacing rates before and 10 minutes after injection of 5 mg atenolol intravenously. Coronary angiography was performed in all patients.

Atenolol reduced resting myocardial blood flow by 16 per cent ($P < 0.001$) and oxygen consumption by 17 per cent ($P < 0.001$). Flow was reduced whether or not the part of myocardium in question was supplied by a stenotic artery. Coronary arteriolar resistance increased by 23 per cent ($P < 0.001$). Myocardial arteriovenous oxygen difference was not affected. Heart rate and rate-pressure index were reduced in all patients ($P < 0.001$). When the heart rate was kept constant by atrial pacing there was no change in the rate-pressure index and no change in any of the coronary haemodynamic values. A small but highly significant increase of 2 mmHg \pm 0.4 (SEM) in left ventricular filling pressure was observed at rest ($P < 0.001$), and 4 mmHg \pm 0.7 ($P = 0.001$) during submaximal pacing. In all three situations the flow per unit left ventricular pressure work was identical before and after atenolol.

It is concluded that the decrement in myocardial blood flow and oxygen consumption effected by the drug could be attributed solely to the reduction in left ventricular work. No direct effect on coronary resistance could be identified. By reducing left ventricular work atenolol will be effective in the treatment of ischaemic heart disease. Since it increases left ventricular filling pressure it must be used with care in patients with latent heart failure.

The beneficial effect of beta-adrenergic blockade in the treatment of angina pectoris is well documented, though the mode of action has been a matter of debate.

A new beta blocker, atenolol (ICI 66 082, 'Tenormin'), has recently been introduced. Preliminary animal studies have shown that it is a selective inhibitor of beta₁-receptors without intrinsic sympathomimetic or membrane stabilising effects. It is as potent as propranolol in antagonising the positive chronotropic response to isoprenaline and stimulation of the cardioaccelerator nerve in the cat, but is less effective in antagonising lipolysis in adipose tissue (Barrett *et al.*, 1973).

Clinical studies in patients with ischaemic heart disease have shown that atenolol reduces significantly the frequency of anginal attacks (Roy *et al.*,

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1975). However, detailed information on its effects on cardiac function in man has not been available. The aim of this investigation was to test the effect of the drug on coronary haemodynamics at rest and at a submaximal stress test, in patients with angina pectoris.

Subjects and methods

PATIENTS

Fifteen patients (1 woman and 14 men) with angina pectoris and without evidence of additional myocardial or valvular heart disease were studied, mean age 47 years \pm 7 (SD). All were sufficiently incapacitated by angina to warrant consideration for coronary bypass surgery. None of the subjects showed clinical signs of heart failure and the heart size was normal as judged by x-ray examination.

Three of the patients had only minor coronary pathology while the rest had significant (more than 50%) stenosis of at least one of the three main coronary arteries. Three patients had stenosis of 1, 4 of 2, and 5 of all 3 arteries. Eight patients had a normal left anterior descending artery, while 7 had a significant stenosis of this vessel. Left ventricular ejection fraction exceeded 50 per cent in all the patients. None of the patients was treated with beta-blocking agents and no other drugs were given during the 24 hours before the investigation. They were examined in the supine position after pre-medication with 0.1 g aprobarbitone. Informed consent was obtained from all the participants.

CATHETERISATION

A special reshaped 7 F two-thermistor thermodilution catheter with pacing electrodes was positioned in the great cardiac vein in the depth of the coronary sinus, through a left antecubital vein. The position was initially assessed by injection of a small amount of contrast material and controlled by fluoroscopy repeatedly throughout the investigation. A 7 F Courmand catheter was placed in the pulmonary artery and a polyethylene catheter inserted into the thoracic aorta.

MEASUREMENTS

Cardiac venous flow was measured by the continuous infusion thermodilution method (Ganz *et al.*, 1971). For this purpose a 0.9 per cent saline solution at room temperature was infused into the great cardiac vein with a Harvard infusion pump at a constant rate of 36 ml/min for 20 to 30 seconds. This method has been found to be reliable for determination of great cardiac venous blood flow in our laboratory with a mean difference between duplicate measurements performed within 1 minute of 3.6 per cent of mean flow (Simonsen, 1977). Pressures were measured by Elema—Schönander EMT 35 transducers and recorded on a Mingograph 800 ink-jet recorder. Ten consecutive beats were analysed and the average pressures were used. Mean pressures were obtained by electrical integration. Aortic stenosis was excluded at left ventricular catheterisation and systolic aortic pressure was, therefore, taken as left ventricular systolic pressure. Cardiac output was determined by the direct Fick method.

PROCEDURE

When all catheters were positioned the patient's angina threshold was tested. This was done by pacing from the cardiac vein, using a Medtronic external pacemaker, at a slowly increasing frequency until unmistakable angina was experienced by the

patient. Then a period of complete rest of 15 minutes was allowed before the measurements were started. Cardiac venous flow was then measured at resting conditions, at a pacing frequency about 10 per minute above resting heart rate and at a submaximal rate 10 per minute below the rate producing angina pectoris. Blood samples were withdrawn from the cardiac vein and aorta immediately before each flow measurement while pressures were recorded simultaneously. Cardiac output was measured only at the two pacing procedures. Ten minutes after an injection of 5 mg atenolol had been given intravenously the complete procedure was repeated.

CALCULATIONS

Great cardiac venous blood flow was calculated from the formula

$$F_I \times 1.19 \left(\frac{T_B - T_I}{T_B - T_M} - 1 \right)$$

where T_B , T_I , and T_M represent the temperature of blood, injectate, and mixture of blood and injectate, respectively. F_I is the volume of injectate and 1.19 is a constant derived from the density and specific heat of saline solution and blood (Ganz *et al.*, 1971).

Myocardial oxygen consumption = (arterial cardiac venous oxygen content) \times cardiac venous flow.

Heart rate pressure index = heart rate per min \times peak systolic aortic pressure.

Left ventricular minute work =

$$\frac{CO (A_o - LVFP) \times 13.6}{1000}$$

where CO is cardiac output, A_o is peak aortic pressure, and LVFP is left ventricular filling pressure (represented by the diastolic pulmonary arterial pressure).

Coronary arteriolar resistance = mean aortic pressure divided by cardiac venous flow.

Statistical analysis was performed using standard procedures. Student's *t* test for paired comparison was used when observations before were compared with those after atenolol. Differences were regarded as significant when $P < 0.05$.

Results

The effect of atenolol on coronary haemodynamics is presented in Table 1 and that on general haemodynamics in Table 2.

OBSERVATIONS AT REST

A reduction in great cardiac venous blood flow

Table 1 Coronary haemodynamic variables before and after 5 mg atenolol intravenously

		Rest	Slow pacing	Submaximal pacing
Great cardiac venous blood flow (ml/min)	B	89 (10)	105 (12)	135 (15)
	A	75 (8)	109 (13)	132 (15)
		P < 0.001	NS	NS
Myocardial arteriovenous oxygen difference (%)	B	59 (1.9)	58 (1.5)	59 (1.3)
	A	60 (2.1)	58 (1.7)	59 (1.7)
		NS	NS	NS
Myocardial oxygen consumption (ml/min)	B	9.6 (0.9)	11.0 (1.1)	14.6 (1.5)
	A	8.0 (0.8)	11.4 (1.2)	14.0 (1.4)
		P < 0.001	NS	NS
Coronary arteriolar resistance (mmHg/ml per min)	B	1.3 (0.1)	1.2 (0.2)	1.0 (0.2)
	A	1.6 (0.2)	1.2 (0.1)	1.0 (0.1)
		P = 0.001	NS	NS
Flow/rate-pressure index $\times 10^{-3}$ (ml/mmHg-beats)	B	9.5 (1.2)	9.5 (1.1)	9.0 (1.1)
	A	9.2 (1.1)	9.8 (1.3)	9.0 (1.1)
		NS	NS	NS
Flow/left ventricular minute work (ml/g m)	B	—	9.2 (1.2)	10.0 (1.4)
	A	—	10.7 (1.3)	11.4 (1.5)
			NS	NS
Myocardial oxygen consumption/rate-pressure index $\times 10^{-4}$ (ml/mmHg-beats)	B	10.3 (1.2)	9.9 (1.1)	9.7 (1.1)
	A	10.0 (1.2)	10.3 (1.2)	9.5 (1.1)
		NS	NS	NS
Myocardial oxygen consumption/left ventricular minute work (ml/g m)	B	—	9.7 (1.2)	10.6 (1.5)
	A	—	11.5 (1.4)	12.1 (1.4)
			NS	NS

Mean values (\pm SEM) and the significance of differences are given. B, before; A, after; NS, not significant, i.e. $P > 0.05$.

Table 2 General haemodynamic variables before and after 5 mg atenolol intravenously

		Rest	Slow pacing	Submaximal pacing
Heart rate (beats/min)	B	74 (3)	82 (2)	110 (2)
	A	63 (3)	82 (2)	110 (2)
		P < 0.001	NS	NS
Systolic aortic pressure (mmHg)	B	133 (5)	137 (5)	140 (5)
	A	133 (5)	139 (5)	138 (5)
		NS	NS	NS
Diastolic pulmonary artery pressure (mmHg)	B	6 (0.4)	6 (0.5)	7 (0.7)
	A	8 (0.5)	9 (0.8)	11 (1.2)
		P < 0.001	P = 0.002	P = 0.001
Cardiac index (l/min)	B	—	3.6 (0.2)	3.8 (0.2)
	A	—	3.5 (0.2)	3.8 (0.2)
			NS	NS
Stroke volume (ml)	B	—	81 (3)	65 (3)
	A	—	80 (4)	64 (3)
			NS	NS
Rate-pressure index $\times 10^{-3}$ (mmHg-beats/min)	B	9.7 (0.4)	11.1 (0.3)	15.4 (0.7)
	A	8.3 (0.4)	11.3 (0.4)	15.2 (0.6)
		P < 0.001	NS	NS
Left ventricular minute work (g m)	B	—	11.8 (0.5)	12.6 (0.6)
	A	—	11.6 (0.7)	12.1 (0.7)
			NS	NS

Mean values (\pm SEM) and the significance of differences are given. B, before; A, after; NS, not significant, i.e. $P > 0.05$.

was noted in all patients averaging 16 per cent ($P < 0.001$). The mean reduction in flow was 18 per cent in the patients where the left anterior descending artery was normal compared with 12 per cent in those with stenosis of this vessel ($P > 0.05$). In 13 of the subjects the myocardial oxygen consumption was reduced. In 2, in whom only a very small reduction in blood flow took place, there was a minute increase in oxygen consumption caused by a small increase in arteriovenous oxygen difference. Overall there was a highly significant fall with a mean of 17 per cent ($P < 0.001$). Coronary arteriolar

resistance increased by 23 per cent ($P < 0.001$) while the arteriovenous oxygen difference remained unchanged. Heart rate was reduced in all patients (mean 11 beats per min ($P < 0.001$)). Aortic systolic pressure did not change, but as a result of the fall in heart rate, the rate-pressure index was significantly reduced after atenolol ($P < 0.001$). The mean reduction in rate-pressure index was 21 per cent in the patients with normal, compared with 10 per cent in those with stenosed left anterior descending artery. Flow per unit rate-pressure index is, however, equal in the 2 groups. The individual changes

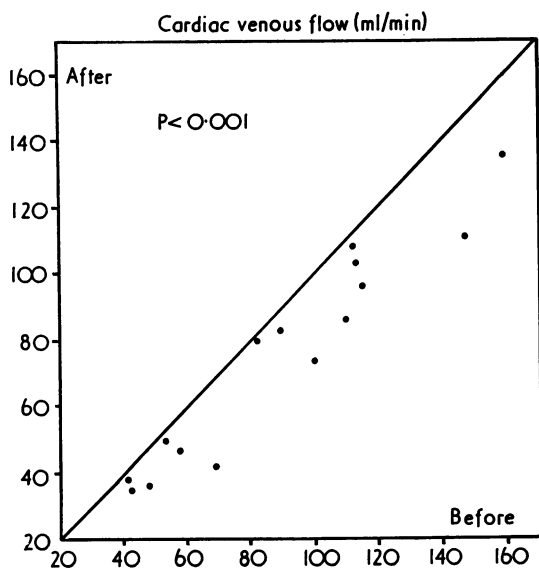


Fig. 1 Cardiac venous flow before and after atenolol.

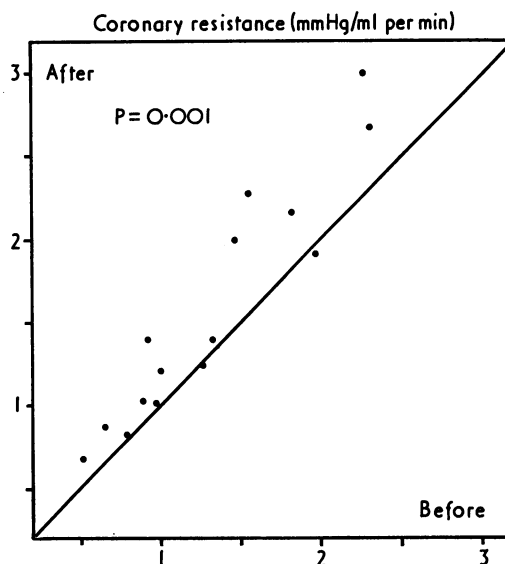


Fig. 3 Coronary resistance before and after atenolol.

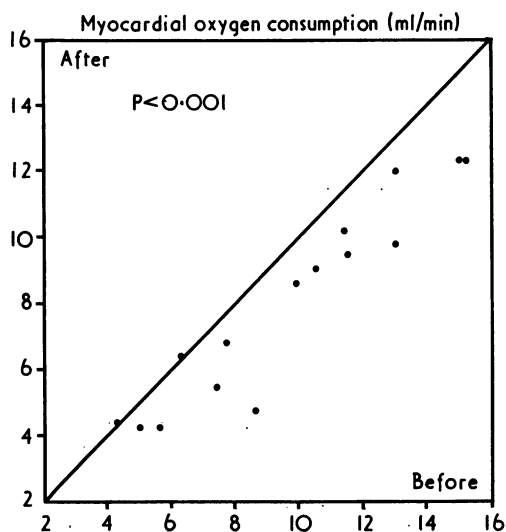


Fig. 2 Myocardial oxygen consumption before and after atenolol.

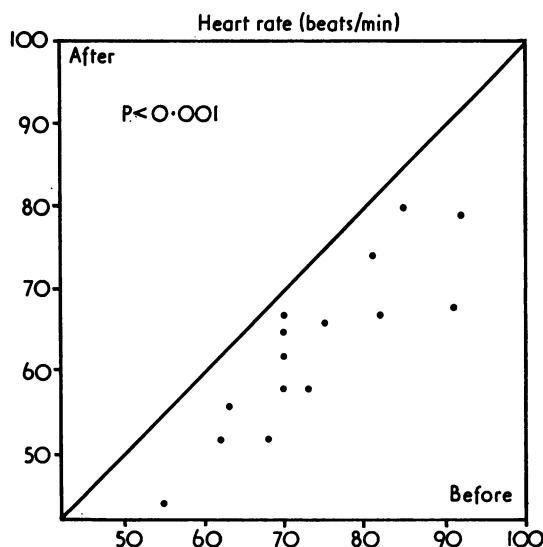


Fig. 4 Heart rate before and after atenolol.

in flow, myocardial oxygen consumption, coronary arteriolar resistance, heart rate, and rate pressure index for all the patients are graphically presented in Fig. 1 to 5. The diastolic pulmonary arterial pressure showed a mean increase of $2 \text{ mmHg} \pm 0.4$. Though numerically small the increase was consistent (Fig. 6) and statistically significant ($P < 0.001$). The increase is, in the absence of mitral valvular disease, taken to represent an increase in left ventricular

filling pressure. The relation between myocardial blood flow per unit work and oxygen consumption per unit work showed no significant change after atenolol.

OBSERVATIONS DURING ATRIAL PACING

Both at the slow and the submaximal pacing rates the coronary haemodynamic variables were constant. Atenolol did not significantly change myo-

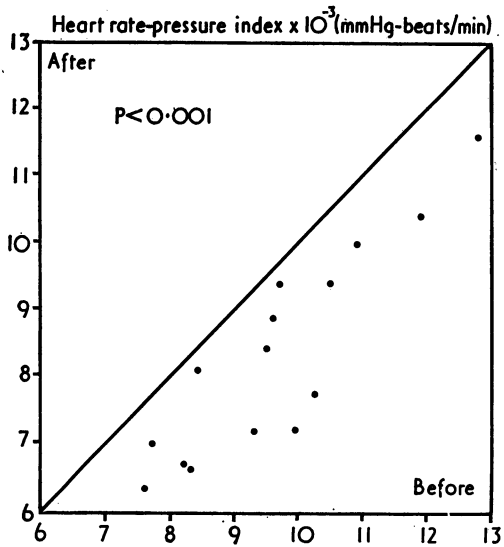


Fig. 5 Heart rate pressure index before and after atenolol.

cardial blood flow, oxygen consumption, or coronary arteriolar resistance. There was no difference in the effects on patients with and patients without stenosis of the left anterior descending artery. The general haemodynamic values showed only small changes. The same heart rate was obtained in all patients except one who at the submaximal pacing rate developed a second degree atrioventricular

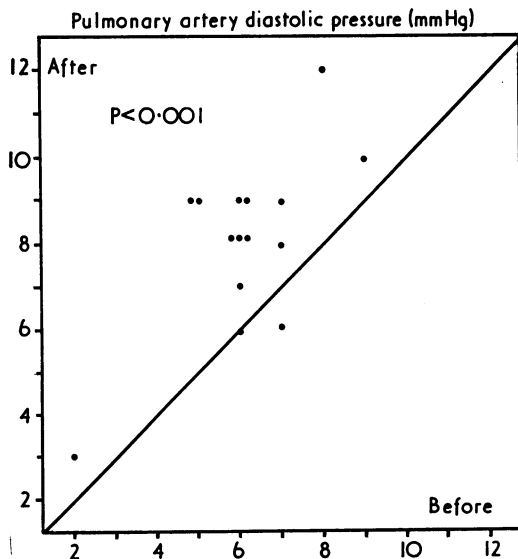


Fig. 6 Pulmonary artery diastolic pressure before and after atenolol.

block after administration of the drug. He was, therefore, excluded from all calculations affected by this feature. Systolic aortic pressure, cardiac output, and the derived values for cardiac work, rate-pressure index, and left ventricular minute work, were not significantly altered. However, as at rest, there was a small but highly significant increase in diastolic pulmonary arterial pressure. At the slow pacing the increase was $2 \text{ mmHg} \pm 0.6$ (SEM) ($P < 0.001$) and at the submaximal pacing $4 \text{ mmHg} \pm 0.7$ ($P = 0.001$). The relation between myocardial blood flow (and oxygen consumption) and left ventricular work was unchanged by atenolol.

Discussion

The present study has shown a reduction in myocardial blood flow and oxygen consumption and an increased coronary arteriolar resistance after atenolol. This supports previous work describing a reduction in flow after application of other selective (Mocchetti *et al.*, 1972) as well as non-selective beta-adrenergic blockers (Wolfson *et al.*, 1966; Stein *et al.*, 1968; Mueller *et al.*, 1974). However, the opposite effect has also been described (Bussmann *et al.*, 1970).

The explanation for these findings must be sought among effects on determinants of myocardial oxygen consumption and possible direct effects on the coronary arteries.

The myocardial oxygen consumption at rest was reduced by atenolol parallel to a reduction in heart rate. By keeping the heart rate constant before and after the drug a stable haemodynamic state was achieved. There was no significant change in systolic aortic pressure and, therefore, the rate-pressure index remained unaltered. Thus, one of the main determinants of myocardial oxygen demand (Jørgensen *et al.*, 1973; Nelson *et al.*, 1974) was constant and oxygen consumption and myocardial blood flow remained unchanged. Considering blood flow and oxygen consumption per unit left ventricular work there was no change after atenolol in any of the 3 experimental situations. This shows that the mechanism responsible for the diminished blood flow at rest was probably a reduction in left ventricular work. Since the metabolic requirements of the myocardium were reduced, myocardial blood flow fell proportionately. This is in agreement with what has been previously shown for other beta-blockers in animal experiments (Stein *et al.*, 1968; Marchetti *et al.*, 1972) and in man (Wolfson and Gorlin, 1969). When, however, as shown in the present study, the work is increased again to pretreatment levels the flow increases in proportion.

The coronary arteriolar resistance at rest increased significantly after atenolol. The reduced flow could, therefore, be explained by an inhibition of sympathetic vasodilator tone as suggested for other beta-blockers (Klocke *et al.*, 1965; Parratt and Grayson, 1966). If this is a primary effect of the drug one would expect increased coronary arteriolar resistance and decreased flow also when myocardial oxygen demand is kept at the same level as before the beta-blockade. No change occurred after selective beta-blockade with atenolol under these circumstances. It has also been shown that the coronary arteries of the dog dilate to the same extent in response to temporary coronary occlusion before and after non-selective beta-blockade (Marchetti *et al.*, 1972). The present study shows that atenolol does not affect the ability of the human coronary arteries to dilate in response to an increase in myocardial oxygen demand. This is so both at low and submaximal levels of left ventricular work, and confirms an earlier study (Stephens *et al.*, 1976) in which atenolol was found not to give rise to coronary vasoconstriction. It has been shown (Pitt and Craven, 1970) that beta-blockade with propranolol alters the distribution of intramyocardial blood flow in the dog so that flow is selectively reduced to non-ischaemic areas. Other workers (Wolfson and Gorlin, 1969) have suggested that the action of propranolol in man may result in a more equitable distribution of coronary flow. This was assumed to occur if collateral vessels supplying ischaemic zones arose proximal to the arteriolar resistance bed and did not contain adrenergic receptors. Collaterals would then be given a selective advantage regarding perfusion when undiseased arterioles were constricted because of unopposed alpha effect after beta-blockade. The great cardiac vein drains the anterolateral left ventricular wall and the anterior part of the interventricular septum, in general the same area which gets its arterial supply through the left anterior descending artery. In the present study blood flow was reduced whether or not there was stenosis on this artery. There was, however, a smaller reduction in flow from the myocardium supplied by a stenotic artery. Flow per unit work was, however, equal in the two groups of patients. The smaller reduction in rate pressure index in the patients with left anterior descending artery stenosis seems, therefore, to be the most likely explanation for the difference in flow observed.

The increase in pulmonary arterial diastolic pressure after atenolol is presumed to reflect an increased left ventricular filling pressure. The drug may, therefore, increase ventricular wall tension and the diastolic volume of the heart as has been shown for other beta-blockers (Chamberlain, 1966;

Swanton *et al.*, 1976) and thus increase myocardial oxygen demand (Simaan, 1974) which would tend to increase myocardial blood flow. Myocardial contractility was not measured in the present investigation, but has been shown to be decreased after atenolol (Stephan *et al.*, 1976) and this reduces oxygen consumption. These effects are small and probably balance one another since there is in all investigations a close relation between flow and pressure work.

The reduction in determinants of myocardial oxygen consumption seen in the present study after atenolol has also been seen during physical exercise (Åström and Vallin, 1974). This explains why it is an effective antianginal drug. The effect on the left ventricular filling pressure indicates, however, that in common with all beta-adrenergic blocking agents, it must be used with care in patients with latent heart failure.

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