THE EFFECT OF PINDOLOL ON MYOCARDIAL BLOOD FLOW, METABOLISM AND FUNCTION DURING REST AND PACING IN PATIENTS WITH CORONARY HEART DISEASE

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- 1 The study was designed to elucidate further the mechanism by which β -adrenoceptor antagonism with pindolol relieves the symptoms of angina pectoris in patients with coronary heart disease.
- 2 Pindolol administration was associated with an elevated threshold for angina pectoris and improved myocardial lactate metabolism during supraventricular pacing.
- 3 This beneficial effect of pindolol was independent of changes in myocardial blood flow and was not mediated by haemodynamic effects.
- 4 The results suggest that in angina pectoris, in addition to the recognized beneficial effects of β -adrenoceptor blockade, the actions of pindolol also result from, as yet, poorly described phenomena such as redistribution of myocardial blood flow or metabolic effects.

Introduction

The beneficial effect of β -adrenoceptor antagonists in the treatment of angina pectoris is well described (Battock *et al.*, 1969; Gianelly *et al.*, 1967; Grantz *et al.*, 1966; Wolfson & Gorlin, 1969). Furthermore, in addition, a favourable influence on morbidity and mortality following acute myocardial infarction has been reported in controlled long-term studies (Multicentre International Study, 1975; Baber *et al.*, 1980; The Norwegian Multicenter Study Group, 1981).

The influence of β -adrenoceptor blockade on the myocardium has been investigated predominantly in the experimental animal (Hübner *et al.*, 1976; Maroko *et al.*, 1971; Pitt & Caven, 1970; Vatner *et al.*, 1977). However, there is little information on the effect of μ -adrenoceptor blockade on myocardial blood flow, myocardial metabolism and haemodynamic function in patients with coronary heart disease (Lichtlen *et al.*, 1977; Mueller *et al.*, 1974; Stephens *et al.*, 1978; Thompson *et al.*, 1980). This study was carried out to investigate the effects of pindolol on the above mentioned variables both at rest and during atrial pacing.

Methods

This study was carried out using 15 patients aged from 40 to 76 years. All underwent cardiac catheterization and were found to have stenosis of the left

anterior descending artery of more than 70% but with a normal left ventricular ejection fraction ($61 \pm 14\%$). The following measurements were recorded:

1. great cardiac vein blood flow by the continuous thermodilution technique (Ganz *et al.*, 1971).
2. left ventricular pressures invasively
3. regional myocardial oxygen consumption and lactate extraction by simultaneous arterial and coronary venous blood samples,
4. continuous ECG recordings lead V₅.

Recordings were made both at rest and during supraventricular pacing to anginal threshold or AV-block. After pacing, after at least 30 min rest when all variables returned to baseline values, control measurements were repeated. The same procedure was then repeated using the same pacing rate 10 min after infusion of 6 $\mu\text{g/kg}$ body weight of pindolol. Results are expressed as mean $\pm$ s.e. mean. Statistical analysis was performed using a paired Student's *t*-test.

Results

Haemodynamic function

No significant changes in left ventricular systolic pressures were observed during the investigation, whereas left ventricular end diastolic pressure in-

Figure 1 The effect (mean $\pm$ s.d.) of pacing and pindolol on left ventricular pressures and heart rate. R = rest, S = pacing, P = pindolol, SP = pacing and pindolol.

creased during pacing from 14 ± 5 to 25 ± 5 mmHg (mean $\pm$ s.d.) and from 15 ± 7 to 23 ± 10 mmHg in the presence of pindolol and pacing (Figure 1).

As one major determinant of myocardial oxygen uptake, the heart rate pressure double product increased similarly during pacing before pindolol (106 ± 27 to 182 ± 44 mmHg $\times 10^2 \times \text{min}^{-1}$) as well as after pindolol (100 ± 27 to 179 ± 39 mmHg $\times 10^2 \times \text{min}^{-1}$) (Figure 2).

Myocardial blood flow

The elevated myocardial oxygen demand during pacing is reflected by the rise in blood flow in the great cardiac vein by 51% from 73 ± 18 to 111 ± 28 ml/min and 48% from 67 ± 19 to 95 ± 27 ml/min before and after pindolol, respectively (Figure 2).

Myocardial metabolism

Regional myocardial oxygen consumption exhibited the expected increase from 7.2 ± 2.1 to 11.6 ± 3.7 ml/min during pacing. The same trend was observed after pindolol (6.6 ± 2.3 to 9.9 ± 3.9 ml/min). For better assessment of myocar-

Figure 2 Pressure rate double product and great cardiac vein flow (mean $\pm$ s.d.) during pacing and after pindolol (abbreviations as Figure 1).

dial metabolism we determined the myocardial lactate extraction ratio and considered a value below 10% in the presence of typical clinical symptoms as an indication of myocardial ischaemia.

The myocardial lactate extraction ratio decreased significantly from $34 \pm 16\%$ to $-1 \pm 32\%$ during pacing and $26 \pm 15\%$ to $9 \pm 21\%$ after pindolol (Figure 3). Since high standard deviations indicated a very heterogeneous group of patients they were subdivided in one group with normal (group I, $n=8$) and one with abnormal (group II, $n=7$) lactate extraction during pacing (Figure 4).

In group I pacing was followed by a rise in the end diastolic left ventricular pressure from 11 ± 6 to 17 ± 6 mmHg, whereas systolic pressure and lactate extraction remained almost unchanged. Therefore the elevated myocardial oxygen demand as the result of increased wall stress and double product was balanced by an adequate rise in coronary blood flow of 51% (76 ± 22 to 114 ± 31 ml/min). The administration of pindolol was not followed by changes in systolic or end diastolic ventricular pressures. The reduction in great cardiac vein flow in the presence of unchanged lactate extraction is considered to result from a lower myocardial oxygen demand induced by a decrease in heart rate by 12%. During pacing no different trend was observed with pindolol compared to the control.

In group II pacing was also associated with unchanged left ventricular systolic pressure and resulted in elevated end diastolic pressure from 18 ± 7

Figure 3 Metabolic effects (mean $\pm$ s.d.) of pacing and pindolol in 15 patients with coronary heart disease (abbreviations as Figure 1).

to 32 ± 6 mmHg. Pindolol had no effect on the haemodynamic function at rest.

A significant rise in end diastolic pressure from 18 ± 9 to 30 ± 4 mmHg was obtained during pacing. This group was characterized by a significant production of lactate, which averaged -28% , and was reduced in the presence of pindolol to 3% under equivalent pacing conditions. Whereas angina pectoris symptoms were induced in all patients during control pacing, symptoms occurred in only two out of seven patients after the administration of pindolol. This clinical finding was supported by ECG recordings, which exhibited lower ST-segment depressions (mean 0.15 mV).

Discussion

β -adrenoceptor antagonism reduces oxygen demand of the myocardium mainly by reducing heart rate – systolic blood pressure double product and depressing contractility. Heart rate in our study was controlled by atrial pacing before and after pindolol. Since systolic and end diastolic pressures did not change significantly, the improvement in myocardial lactate extraction ratio during pacing in the presence of pindolol occurred without a reduction of the major

Figure 4 Myocardial lactate extraction ratio and great cardiac vein flow (mean $\pm$ s.d.) in patients with normal ($\bullet$, group I, $n = 8$) and abnormal ($\square$, group II, $n = 7$) myocardial lactate extraction ratio. Pindolol improved the myocardial lactate extraction ratio during pacing without altering great cardiac vein flow (abbreviations as Figure 1).

determinants of myocardial oxygen demand, and can therefore not be attributed to haemodynamic changes induced by the drug. Therefore these findings suggest that pindolol may modify myocardial metabolism in addition to its haemodynamic effects.

Wolfson & Gorlin (1969) reported a reduction of myocardial blood flow after propranolol in patients with coronary artery disease both at rest and during exercise. Since this was associated with reduced myocardial oxygen consumption, it was proposed that β -adrenoceptor antagonism promotes a redistribution of myocardial blood flow from non-ischaemic to ischaemic areas (Pitt & Craven, 1970). Facilitated blood flow to the ischaemic myocardium has been suggested as one possible mechanism by which β -adrenoceptor antagonism may relieve angina.

As another mechanism direct effects on the cellular level have to be considered. Thompson *et al.* (1980) observed that changes in myocardial lactate and pyruvate extraction after atenolol were related inversely to changes in arterial free fatty acid concentrations suggesting that the improvement in myocardial metabolism could have been secondary to reduced peripheral lipolysis. This hypothesis is supported by our findings that increased myocardial

lactate extraction was associated with relief of angina in most of our patients in group II, although the rise in end diastolic pressure induced by pacing was not abolished.

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Further investigations are needed to elucidate completely the mechanism by which β -adrenoceptor antagonists exert beneficial effects in patients with angina.