Immediate haemodynamic effects of a beta adrenergic blocking agent – propranolol – in mitral stenosis at fixed heart rates

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Previous haemodynamic studies in our laboratory have shown that pulmonary arterial and arterial wedge pressures in patients with isolated mitral stenosis decreased after administration of propranolol, without significant changes in right heart filling pressures or stroke volume. Reduction of heart rate with consequent prolongation of the diastolic filling period was thought to be the determining factor. These findings have been further confirmed in the present study by evaluating the effect of propranolol in such patients, paced at fixed heart rates. Propranolol produced no significant haemodynamic effects during cardiac pacing. However, the post-pacing pulmonary vascular pressures were significantly reduced. These changes correlated well with reduction of heart rate and prolongation of the diastolic filling period. It appears that the haemodynamic effects of propranolol in patients with mitral stenosis are mainly related to the negative chronotropic effect.

Reduction of left heart filling and pulmonary arterial pressures in patients with mitral stenosis by parenterally administered beta adrenergic blocking agents has been documented by several investigators (Howitt, Tinker, and Wade, 1965; Tsolkas, Davies, and Oram, 1965; Cumming and Carr, 1966; Goyle *et al.*, 1969). It has been, however, suggested that the negative inotropic effects of beta adrenergic blockade, by reducing cardiac output (Howitt *et al.*, 1965; Stavropoulos, Davies, and Gazetopoulos, 1965; Bensaid, Scebat, and Lenegre, 1970), and the increase of ventricular filling pressures (Cumming and Carr, 1966), may negate these beneficial effects. However, in our studies on patients with isolated mitral stenosis (Goyle *et al.*, 1969), the negative chronotropic effect of propranolol appeared to be the dominant factor responsible for the observed circulatory effects. The present study was designed to verify these observations further.

Patients and methods of study

Five patients, 2 men and 3 women, aged 21 to 38 years, with isolated rheumatic mitral stenosis were studied. Four patients were in normal sinus

rhythm. The fifth patient, who was in normal sinus rhythm before cardiac catheterization, developed atrial fibrillation during the early part of the study. No patient was currently receiving digitalis preparations.

A No. 7 French, Goodale Lubin Cardiac catheter was introduced via the right median basilic vein and its tip was manoeuvred into the main pulmonary artery under fluoroscopic control. A NBIH bipolar pacing catheter was introduced through the same or a different right arm vein and placed at a site in the right atrium consistent with complete capture of cardiac rhythm, when paced with an external fixed rate pacemaker. In the patient with atrial fibrillation, cardiac rate was controlled by right ventricular pacing. The right brachial artery was cannulated with a Teflon arterial needle and used as a site for monitoring pressure and for sampling blood dye mixture for recording indicator dilution curves. Dye dilution curves were obtained by injecting Evan's blue dye (5.0 to 7.5 mg) into the pulmonary artery and sampling the blood dye mixture at the peripheral arterial site, through a Colson cuvette densitometer (Model I-103) at a constant withdrawal rate of 25 ml/min. Pressures were obtained using Statham P23Db pressure transducers. Mean pressures were recorded by electronic integration. Baseline for all pressure measurement was at half the chest thickness at second costal cartilage with the patient supine (Roy, Gadboys, and Dow, 1957). All data were recorded photographically on

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an Electronics for Medicine DR-8 multichannel recorder.

Left ventricular pressures were obtained in 3 patients by a retrograde aortic approach using a disposable, preformed catheter. Indirect transmitral pressure gradients in these patients were obtained by simultaneous recording of pulmonary artery wedge and left ventricular diastolic pressures using equisensitive preamplifiers with a common baseline. The maximum rate of rise of left ventricular pressure was obtained with an R-C differentiator (Electronics for Medicine Inc.).

Cardiac output was determined from the dye dilution curves using a semilog replot of the recorded curve (Hamilton *et al.*, 1932). Calculated data were obtained as follows.

$$\text{Stroke index (ml/beat/m}^2\text{)} = \frac{\text{Cardiac index (ml/min/m}^2\text{)}}{\text{Heart rate (beats/min)}}$$

$$\text{Vascular resistance (units)} = \frac{\text{Arterial mean pressure (mmHg)} - \text{Atrial mean pressure (mmHg)}}{\text{Cardiac index (l./min/m}^2\text{)}}$$

$$\text{Systolic ejection rate (ml/sec/m}^2\text{)} = \frac{\text{Cardiac index (ml/min/m}^2\text{)}}{\text{Systolic ejection period (sec/min)}}$$

$$\text{Left ventricular work index (kg m/min/m}^2\text{)} = \frac{\text{Left ventricular systolic mean pressure (mmHg)} - \text{left ventricular filling pressure (mmHg)} \times \text{cardiac index (l./min/m}^2\text{)} \times 1.36}{100}$$

$$\text{Stroke power (g m/sec/m}^2\text{)} = \frac{\text{Left ventricular work index (kg m/min/m}^2\text{)}}{\text{Systolic ejection period (sec/min)}}$$

$$\text{Left ventricular stroke work index (g m/beat/m}^2\text{)} = \frac{\text{Left ventricular work index (kg m/min/m}^2\text{)}}{\text{Heart rate (beats/min)}}$$

Data obtained were statistically evaluated using the students 't' test.

Plan of study Patients were studied without sedation or anaesthesia in a postabsorptive state. After recording control data, including dye dilution curves, cardiac pacing was initiated and maintained for 5 minutes, when a second set of pressures and cardiac flow was recorded and pacing continued. Five mg propranolol was injected over a 5-minute period through the indwelling catheter into the pulmonary artery. Fifteen minutes after the midpoint of drug administration, a third similar set of data was obtained. Cardiac pacing was then stopped and 10 minutes later the final set of pressures and cardiac output was recorded.

Results

Heart rate, cardiac index, stroke index, and diastolic filling period (Table 1, 2, 3, and Fig. 1) Resting heart rate of 75 to 108/min (mean 91/min) was increased to 96/120

min (mean 106 min) by cardiac pacing to achieve cardiac control. The post-pacing heart rate of 65 to 78 min (mean 71 beats/min) under the effect of propranolol was significantly lower than the paced heart rate ($P < 0.01$).

No consistent change in cardiac index was noted with pacing. It was also unaffected by administration of propranolol while the heart was paced but decreased to 2.9 l./min/m² after stopping cardiac pacing, a statistically significant change from the pacing value ($P < 0.01$).

Pacing before and after propranolol administration resulted in almost identical stroke indices (36.1 and 37.2 ml/beats/ml²), a value lower than the control stroke index (40.6 ml/beat/m²). However, the post-pacing stroke index under the effect of beta adrenergic blockade was almost the same (41.1 ml/beat/m²) as the control stroke index.

With changes in heart rate, the diastolic filling period per beat was insignificantly reduced, the control diastolic filling period of 0.390 sec/beat, decreasing to 0.329 and 0.335 sec/beat respectively during pacing, before and after administration of propranolol. However, conspicuous prolongation of this interval was noted (mean 0.529 sec/beat) in the post-pacing period ($P < 0.01$).

Pulmonary artery, pulmonary arterial wedge, left ventricular (diastolic) pressures, transmitral pressure gradient, and pulmonary vascular resistance (Table 1, 2, 3; Fig. 2, 3, and 4) Mean pulmonary artery pressure during cardiac pacing (29.7 mmHg) was almost the same as control (26.6 mmHg). It was unchanged by propranolol at a fixed paced heart rate. However, a significant reduction (mean 21.3 mmHg $P < 0.01$) was noted after stopping pacing.

Pulmonary arterial wedge pressure was also slightly increased during pacing. It was, however, unaffected by propranolol while pacing was continued. However, when cardiac pacing was terminated, pulmonary wedge pressure decreased significantly ($P < 0.02$) as compared to the paced value.

Reduction of pulmonary arterial wedge pressure was closely related to changes in heart rate and diastolic filling period (Fig. 4), but not to changes of blood flow across the mitral valve.

A variable change in pulmonary vascular resistance occurred during cardiac pacing both before and after administration of propranolol. Likewise, the post-pacing pulmonary vascular resistance was variably changed (increased in two patients, and slightly decreased

TABLE I Effects of propranolol in mitral stenosis at fixed heart rate (haemodynamic data)

Case No.	Age (yr)	Heart rate (beats/min)				Pulm. artery mean pressure				Pulm. artery wedge mean pressure				Brachial artery mean pressure			
		R	P	P+I	I	R	P	P+I	I	R	P	P+I	I	R	P	P+I	I
1	25 M	85	96	96	—	32.0	36.0	35.0	—	25.0	24.0	24.0	—	66.0	67.0	62.0	—
2	35 F	108	110	110	78	18.0	17.5	14.0	12.0	13.0	12.5	11.0	8.5	90.0	81.0	89.0	94.0
3*	28 M	96	120	120	70	32.0	38.0	40.0	31.0	23.0	29.0	27.0	19.0	80.0	98.0	118.0	105.0
4	21 F	75	100	100	65	25.0	30.0	32.0	21.0	20.0	25.0	27.0	17.0	80.0	—	—	84.0
5	38 F	90	105	105	72	26.0	27.0	25.0	21.0	21.0	22.5	21.0	16.0	84.0	78.0	78.0	72.0
	Mean	90.8	106.2	106.2	71.3	26.6	29.7	29.2	21.3	20.4	22.6	22.0	15.1	80.0	81.0	86.8	88.8
	SD	12.3	9.3	9.3	5.4	5.8	7.9	10.1	7.8	4.2	6.1	6.6	4.3	7.6	12.8	23.6	13.0

I, data obtained 10 minutes after stopping pacing; P, data obtained 5 minutes after fixed rate cardiac pacing; P+I, data obtained 15 minutes after injection of propranolol and continued pacing; R, control resting data.
* Patient with atrial fibrillation and right ventricular pacing.

FIG. 1 Shows the effect of propranolol on heart rate (HR), stroke index (SI), and diastolic filling period (DFP), during fixed rate cardiac pacing in patients with mitral stenosis. Propranolol (PNG+PRL) did not affect the stroke index of paced (PNG) patients. However, after stopping pacing (PRL) stroke index increased in all instances. A conspicuous prolongation of diastolic filling period (DFP) also occurred when pacing was stopped after injection of propranolol, while during pacing it caused no such change (C, control data).

in another and decreased in the fourth patient) as compared to pacing values.

Left ventricular end-diastolic pressure (Fig. 3), which was normal at rest in 2 of the 3 patients, decreased with pacing in all instances and was unaffected by propranolol while pacing was continued. Furthermore, the left ventricular end-diastolic pressure was insignificantly changed when pacing was stopped and only the effects of propranolol were still manifest.

A significant pressure gradient across the mitral valve present at rest increased slightly further with cardiac pacing before and after propranolol administration, but decreased in all instances to either control or even lower levels in the post-pacing phase. However, all these changes were of no statistical significance.

Discussion

The raised left atrial pressure in patients with mitral stenosis is related to several factors, of which the size of the mitral orifice, flow across the valve during diastole, the duration of the diastolic filling period, and the left ventricular diastolic pressures are most important. In an individual patient the size of mitral orifice being fixed, left atrial pressure would be related to the latter factors and an increased blood flow, a decreased diastolic filling period, and an increase in left ventricular diastolic pressure would all lead to an increased pressure in the left atrium and vice versa. Beta adrenergic blocking agents, because of the negative inotropic and chronotropic effects, may be expected to reduce flow and increase the diastolic filling period with consequent reduction of left atrial and pulmonary arterial

LV end-diastolic				Pulm. artery wedge - LV end-diastolic				Cardiac index (l./min/m ²)				Stroke index (ml/beat/m ²)			
R	P	P+I	I	R	P	P+I	I	R	P	P+I	I	R	P	P+I	I
—	—	—	—	—	—	—	—	—	4.2	4.8	—	—	44.0	50.0	—
—	—	—	—	—	—	—	—	3.4	3.4	3.3	2.8	31.5	31.0	30.0	36.0
15.0	12.0	11.5	11.5	8.0	13.0	14.0	8.5	2.5	3.8	4.0	2.8	39.0	31.5	33.0	40.0
8.0	5.0	8.0	8.0	15.0	25.0	22.0	10.0	3.7	4.0	4.1	3.4	50.0	40.0	41.0	52.5
9.0	7.5	6.5	9.8	14.5	17.0	15.0	8.0	3.8	3.6	3.3	2.6	42.0	34.0	32.0	36.0
10.7	8.2	8.7	10.0	12.5	18.3	17.0	8.8	3.4	3.8	3.9	2.9	40.6	36.1	37.2	41.1
3.8	3.5	1.5	2.0	4.0	6.1	4.4	1.0	0.6	0.3	0.6	0.3	7.5	5.6	8.3	8.1

FIG. 3 Left ventricular end-diastolic pressure (LVED) decreased slightly during pacing at fixed heart rate (PNG) and was insignificantly reduced by propranolol during fixed rate cardiac pacing (PRL+PNG) in 2 of the 3 patients. In the third patient left ventricular end-diastolic pressure increased after propranolol (Case 5). The final pressures achieved were within the normal range.

pressure. Such an effect has been seen in man by several investigators (Howitt *et al.*, 1965; Tsolkas *et al.*, 1965; Cumming and Carr, 1966; Goyle *et al.*, 1969). However, the role of each of these factors in reducing these pressures is not precisely defined since alterations of diastolic flow and diastolic filling period per beat subsequent to the administration of beta adrenergic blocking drugs have been variable in the experience of different investigators. Thus, Bishop and Segel (1963), Cumming and Carr (1966), and Howitt *et al.* (1965) observed no change of stroke volume. Stavropoulos *et al.* (1965) and Bensaid *et al.* (1970) noted a consistent though small reduction, and Tsolkas *et al.* (1965) found a universal increase of stroke volume after beta adrenergic blockade. Similarly the diastolic filling period has been reported to be unaffected by beta adrenergic blockage in patients with mitral stenosis by Tsolkas *et al.* (1965), and Cumming and Carr (1966), and increased only in patients with atrial fibrillation by Howitt *et al.* (1965).

Our results of the immediate haemodynamic effects of propranolol in patients

FIG. 2 Pacing caused slight increase of pulmonary artery (P_A) and pulmonary artery wedge mean (P_{AW}) pressures. This was variably but insignificantly altered by propranolol at fixed heart rates. However, after stopping cardiac pacing, a steep fall of both P_A and P_{AW} pressure was evident. Pulmonary vascular resistance (PVR) was variably altered.

TABLE 2 *Effects of propranolol in mitral stenosis at fixed heart rate (haemodynamic data)*

Case	Age (yr) sex	LV work index (kg m/min/m ²)				LV stroke work index (g m/beat/m ²)				LV or aortic* dp/dt (mmHg/sec)				Diastolic filling period (sec/beat)			
		R	P	P+I	I	R	P	P+I	I	R	P	P+I	I	R	P	P+I	I
1	25 M	—	4.1	4.3	—	—	43.0	45.0	—	—	720*	463*	—	—	0.393	0.400	—
2	35 F	4.6	4.2	4.3	3.6	42.5	38.0	39.0	47.0	1450*	860*	688*	682*	0.317	0.332	0.334	0.530
3†	28 M	—	6.0	5.9	4.1	—	50.0	49.0	59.0	1730	1536	1030	1363	0.400	0.302	0.300	0.571
4	21 F	3.9	4.8	5.0	4.3	52.0	48.0	50.0	65.0	1164	811	1008	988	0.440	0.300	0.280	0.500
5	38 F	4.3	4.3	3.5	2.8	48.0	41.0	33.5	39.0	1350	1440	1440	1080	0.404	0.316	0.309	0.514
	Mean	4.3	4.7	4.6	3.7	47.5	44.0	43.3	52.5	1424	1073	926	1028	0.390	0.329	0.335	0.529
	SD	0.4	0.8	0.9	0.7	4.5	4.9	6.9	11.7	236.2	383.3	371.7	280.6	0.051	0.038	0.046	0.044

*Patients in whom aortic dp/dt has been recorded.

† Patient with atrial fibrillation paced from the right ventricle.

TABLE 3 *Effect of propranolol in mitral stenosis at fixed heart rate (statistical data)*

	Resting		Pacing		P	Pacing		Pacing with propranolol		P
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Heart rate/min.	90.8	12.3	106.2	9.3	<0.05	106.2	9.3	106.2	9.3	NS
Pulm. art. mean (mmHg)	26.6	5.8	29.7	7.9	NS	29.7	7.9	29.2	10.1	NS
Pulm. art. wedge mean (mmHg)	20.4	4.2	22.6	6.1	NS	22.6	6.1	22.0	6.6	NS
Brachial art. mean (mmHg)	80.0	7.6	81.0	12.8	NS	81.0	12.8	86.8	23.6	NS
Left vent. end-diast. (mmHg)	10.7	3.8	8.2	3.5	NS	8.2	3.5	8.7	1.5	NS
Pulm. art. wedge - LV end-diastolic (mmHg)	12.5	4.0	18.3	6.1	NS	18.3	6.1	17.0	4.4	NS
Cardiac index (l./min/m ²)	3.4	0.6	3.8	0.3	NS	3.8	0.3	3.9	0.6	NS
Stroke index (ml/beat/m ²)	40.6	7.5	36.1	5.6	<0.05	36.1	5.6	37.2	8.3	NS
LV work index (kg m/min/m ²)	4.3	0.4	4.7	0.8	NS	4.7	0.8	4.6	0.9	NS
LV stroke work index (g m/beat/m ²)	47.5	4.5	44.0	4.9	<0.05	44.0	4.9	43.3	6.9	NS
LV or aortic dp/dt (mmHg/sec)	1424	236.2	1073	383.3	NS	1073	383.3	926	371.7	NS
Diastolic filling period (sec/beat)	0.390	0.051	0.329	0.038	NS	0.329	0.038	0.335	0.046	NS
Systolic ejection rate (ml/syst sec)	138.0	17.0	153.0	23.0	NS	153.0	23.0	154.0	40.0	NS
Stroke power (g m/sec/m ²)	168.3	20.1	186.4	38.0	NS	186.4	38.0	181.0	45.0	NS
Pulm. vascular resistance (units)	1.9	1.2	1.8	0.6	NS	1.8	0.6	1.8	0.1	NS
Syst. vascular resistance (units)	24.4	4.3	21.2	5.0	NS	21.2	5.0	22.8	7.1	NS

SD, standard deviation; NS, not significant at 5 per cent level.

with mitral stenosis, with atrial fibrillation, or in normal sinus rhythm have been different and more consistent (Goyle *et al.*, 1969). The resting pulmonary artery and arterial wedge pressures were found to decrease in almost all instances, with no significant change of stroke volume, but a significant prolongation of the diastolic filling period as a consequence of slowing of the heart rate. Data obtained in the present study confirm the importance of the negative chronotropic effect of propranolol in producing the observed haemodynamic effects in patients with mitral valvular obstruction. As long as the heart rate was kept constant by fixed rate pacing, beta adrenergic blockade produced no significant changes of pulmonary arterial or pulmonary arterial wedge pressures. However, the effects became evident in the immediate post-pacing period. Since the stroke volume was, if anything, a little higher at this time, a factor that should

result in an increase of pulmonary pressures, the net decrease indicates that prolongation of the diastolic filling period was the main factor involved in the observed pressure changes. Our findings are in contrast to the recently reported effect of another beta adrenergic blocking agent - oxprenolol - in paced patients with mitral stenosis, reported by Ben-said *et al.* (1970). These investigators observed no significant change of pulmonary arterial mean pressure, a slight reduction of heart rate, but a significant fall of cardiac index ($P < 0.01$) and stroke index ($P < 0.05$). They have suggested that the presence of a fixed obstacle, as in mitral stenosis, unmasks the negative inotropic effects of the drug. The variability of these results in contrast to those observed in our study may be related to the rather high dose of oxprenolol (0.2 mg/kg) used to elicit the response. It is possible that in this high concentration, oxprenolol may

Systolic ejection rate (ml/syst sec)				Stroke power (g m/sec/m ²)				Vascular resistance (units)							
R	P	P+I	I	R	P	P+I	I	Pulmonary				Systemic			
								R	P	P+I	I	R	P	P+I	I
—	190.0	220.0	—	—	180	200	—	—	2.5	2.7	—	—	15.5	12.5	—
136.0	145.0	135.0	150.0	180	180	176	196	1.3	1.5	0.8	1.0	26.0	24.0	27.0	33.0
117.0	160.0	167.0	140.0	—	252	246	205	3.6	2.4	3.2	4.3	29.6	24.2	28.0	35.2
137.0	135.0	128.0	126.0	145	160	156	158	1.3	1.2	1.2	1.2	20.0	—	—	15.4
160.0	135.0	120.0	113.0	180	160	127	120	1.2	1.4	1.2	1.9	22.0	—	23.5	27.5
138.0	153.0	154.0	132.0	168.3	186.4	181.0	169.8	1.9	1.8	1.8	2.1	24.4	21.2	22.8	27.8
17.0	23.0	40.0	16.0	20.1	38.0	45.0	38.0	1.2	0.6	0.1	1.5	4.3	5.0	7.1	8.8

Pacing		Propranolol		P
Mean	SD	Mean	SD	
106.2	9.3	71.3	5.4	<0.01
29.7	7.9	21.3	7.8	<0.01
22.6	6.1	15.1	4.3	<0.02
81.0	12.8	88.8	13.0	NS
8.2	3.5	10.0	2.0	NS
18.3	6.1	8.8	1.0	NS
3.8	0.3	2.9	0.3	<0.01
36.1	5.6	41.1	8.1	NS
4.7	0.8	3.7	0.7	NS
44.0	4.9	52.5	11.7	NS
107.3	383.3	102.8	280.6	NS
0.329	0.038	0.529	0.044	<0.01
153.0	23.0	132.0	16.0	NS
186.4	38.0	169.8	38.0	NS
1.8	0.6	2.1	1.5	NS
21.2	5.0	27.8	8.8	NS

standing rheumatic heart disease or associated coronary or hypertensive heart disease. It is possible that such patients may develop greater depression of myocardial function with beta adrenergic blocking drugs. This suggests a cautious use of these agents in such patients.

FIG. 4 A close correlation exists between heart rate (HR) pulmonary artery wedge pressure (PAW), and diastolic filling period (DFP). During pacing when heart rate and diastolic filling period were constant propranolol had no effect on PAW pressure. Reduction was however noted after pacing was stopped when the negative chronotropic effects of propranolol were manifest, with attendant reduction of heart rate and increased diastolic filling period. Stroke index at this time was unchanged as compared to the control non-paced period, but was higher than during the period of pacing before and after administration of propranolol.

exert a direct myocardial depressant effect besides the specific beta adrenergic receptor blocking effect.

Negative inotropic effects of propranolol have been considered to negate the usefulness of beta adrenergic blocking drugs in mitral stenosis (Cumming and Carr, 1966). However, our data show that neither the right heart filling pressures (Goyle *et al.*, 1969) nor the left ventricular diastolic pressures (present study) are significantly affected in such patients. Such a fear may, therefore, be unwarranted in selected patients.

Variation of our data from that of other investigators may be due to application of more rigid criteria in selection of patients with lone mitral stenosis and exclusion of those with any other valvular lesion. It may also be due to the younger age of these patients without attendant occult coronary heart disease and with possibly a healthier myocardium (Roy *et al.*, 1963). Older patients are likely to have some myocardial disease related to either long-

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