Acute haemodynamic effects of oral prazosin in severe mitral regurgitation^{*†}

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SUMMARY Acute haemodynamic effects of single dose oral prazosin were studied in eight patients with mitral regurgitation. Heart rate, mean systemic arterial pressure, pulmonary arterial pressure, left ventricular filling pressure, and forward cardiac output were measured in all patients. At peak effect, prazosin reduced mean systemic arterial pressure (95 ± 4 to 86 ± 4 mmHg), pulmonary arterial pressure (45 ± 6 to 23 ± 4 mmHg), and left ventricular filling pressure (30 ± 4 to 21 ± 3 mmHg). Pulmonary and systemic vascular resistance also fell (316 ± 49 to 208 ± 43 dynes s cm^{-5} and 2132 ± 148 to 1491 ± 94 dynes s cm^{-5} , respectively). Forward cardiac index increased from 1.89 ± 0.12 to 2.43 ± 0.13 l/min per m^2 and stroke volume from 43 ± 5 to 57 ± 6 ml/beat after prazosin. The onset of these changes occurred between 15 and 30 minutes, peaked between 45 and 60 minutes, and persisted for six hours. These data indicate that in patients with mitral regurgitation oral prazosin promptly improves cardiac performance (judged by increased forward cardiac output and reduced left ventricular filling pressure) as systemic and pulmonary vascular resistances are reduced.

Vasodilator treatment often improves the haemodynamic state of patients with cardiomyopathy.¹⁻⁵ Reduction in systemic vascular resistance results in augmented cardiac output, while a reduction in venous return effects a decline in left ventricular filling pressure. Administration of intravenous nitroprusside, an equipotent dilator of arterial resistance and venous capacitance vessels, increases forward cardiac output in patients with mitral⁶ or aortic regurgitation⁷ in association with a decrease in peripheral vascular resistance. Administration of oral hydralazine improves forward flow in mitral regurgitation and decreases the regurgitation fraction.⁸ Oral prazosin has been shown to exert dilatating effects on arterial and venous beds qualitatively similar to the effects of intravenous nitroprusside.⁹ Prazosin increases cardiac output and decreases left ventricular filling pressure in patients with heart failure.⁹⁻¹¹ The haemodynamic effects of oral prazosin in patients with mitral regurgitation have not been reported.

The purpose of this study was to evaluate the acute effects of oral prazosin on forward cardiac output and left ventricular filling pressure in patients with mitral regurgitation.

Methods

PATIENTS

The study group comprised eight men (aged 24 to 65 years) with severe mitral regurgitation. At the time of study, all subjects were in the New York Heart Association¹² functional class III or IV. Three of these patients also had coronary heart disease documented by history, electrocardiograms, and coronary angiography. None had angina at the time of study. No localised abnormalities were observed on the left ventriculogram. Angiographically, the severity of mitral regurgitation varied from 3+ to 4+. Six of these patients were receiving digitalis and diuretics: digitalis was continued but diuretics were withdrawn two days before the study. None of the patients was taking nitrates or other vasodilators.

HAEMODYNAMIC STUDIES

The procedure was carefully explained to all

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patients and informed consent was given by them. They were kept in bed for at least eight hours before the study to achieve a steady state, and were moved to a special study room of the cardiac care unit so that haemodynamic variables could be monitored and recorded for long periods.

A triple lumen flow-directed catheter was inserted into the pulmonary artery. A Teflon catheter was placed percutaneously into the radial artery to measure systemic blood pressure. Systemic and pulmonary arterial pressures and pulmonary capillary wedge pressures were recorded on an Electronics for Medicine VR6 recorder with P 231a Statham strain gauge transducers. Mean pressures were obtained by electronic filtration. All pressure measurements were referenced to the mid-chest. Heart rate was averaged from recordings of a standard electrocardiographic lead. Cardiac output was measured in triplicate with the thermodilution technique¹³ using a thermodilution computer (Edwards Laboratory, Santa Ana, California), and the data are reported as the average of these three determinations. All the haemodynamic measurements were made in these patients for eight hours.

CALCULATIONS

The following calculations were made:

$$CI = CO/BSA \text{ l/min per m}^2$$

$$SV = CO/HR \text{ ml/beat}$$

$$LVSWI = SVI \times (\overline{Ao} - LVFP) \times 0.0136 \text{ g m per m}^2$$

$$SVR = \overline{Ao} \times 80/CO \text{ dynes s cm}^{-5}$$

$$PVR = (\overline{PA} - LVFP) \times 80/CO \text{ dynes s cm}^{-5}$$

Where CI = cardiac index, CO = cardiac output, BSA = body surface area, SV = stroke volume, HR = heart rate, SVI = stroke volume

index, LVSWI = left ventricular stroke work index, $\overline{Ao}$ = mean arterial pressure, LVFP = left ventricular filling pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, $\overline{PA}$ = mean pulmonary artery pressure.

STUDY PROCEDURE

Haemodynamic measurements were made repeatedly until a stable state was achieved. The patients were considered to be stable when haemodynamic variables were within 10 per cent on multiple measurements. Each patient was then given a single 4 mg dose of oral prazosin. Haemodynamic data were recorded every 15 minutes for the first hour and then every hour for the additional seven hours.

STATISTICS

Mean and standard error of the mean were calculated. The paired Student *t* test was used to determine the statistical significance of comparisons between the control and peak effect periods. A probability (*p*) value of less than 0.05 was considered significant.

Results

Haemodynamic effects were observed between 15 and 30 minutes after oral prazosin, peaked between 45 and 60 minutes, and persisted for approximately six hours (Table). Changes in haemodynamic variables at peak effect are shown in Fig. 1 to 5.

Heart rate decreased slightly in all but two patients after oral prazosin (92 ± 7 to 88 ± 5 beats/min, *p* = NS). A 9 per cent decline in mean arterial pressure from 95 ± 4 to 86 ± 4 mmHg (*p* < 0.005)

Table Haemodynamic responses in control state, and after prazosin administration

	Heart rate (beats/min)	Pressures (mmHg)			Cardiac index (l/min per m ²)	Stroke volume (ml/min)	LVSWI (g m per m ²)	SVR (dynes s cm ⁻⁵)	PVR (dynes s cm ⁻⁵)
		Mean systemic arterial	Mean pulmonary arterial	Left ventricular filling					
Control									
Mean	92	95	45	30	1.89	43	19.6	2132	316
± SEM	7	4	6	4	0.12	5	2.7	148	49
Peak effect (1 to 6 h) of prazosin									
Mean	88	86	33	21	2.43	57	26.7	1491	208
± SEM	5	4	4	3	0.13	6	3.8	94	43
Eight hours after prazosin									
Mean	90	92	40	26	2.12	51	22.1	1653	269
± SEM	6	5	5	4	0.13	7	3.9	112	54

LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

was observed (Fig. 1). Cardiac index increased from 1.89 ± 0.12 to 2.43 ± 0.13 l/min per m^2 ($p < 0.001$). Stroke volume increased from 43 ± 5 to 57 ± 6 ml/beat ($p < 0.001$). Increases in cardiac index and stroke volume were observed in each patient (Fig. 2). Left ventricular stroke work index also increased in each patient (mean 19.6 ± 2.9 to 26.7 ± 3.8 g m per m^2 ($p < 0.01$)).

A significant decline in mean pulmonary artery pressure from 45 ± 6 to 33 ± 4 mmHg ($p < 0.02$) occurred. Left ventricular filling pressure decreased from 30 ± 4 to 21 ± 3 mmHg ($p < 0.01$). These changes in mean pulmonary artery and left ventricular filling pressures were noticed in each patient studied (Fig. 3). The "v" wave in the pulmonary artery wedge pressure tracing gradually decreased in each patient from a mean of 40 ± 6 to 20 ± 4 mmHg ($p < 0.001$). The gradual decline in "v" wave after prazosin administration in a patient is shown in Fig. 4.

Systemic and pulmonary vascular resistance decreased in each patient studied with a single dose of prazosin. At peak effect, systemic vascular resistance was reduced from 2132 ± 148 to 1491 ± 94 dynes cm^{-5} ($p < 0.001$). Similarly, pulmonary vascular resistance declined from 316 ± 49 to 208 ± 43 dynes cm^{-5} ($p < 0.005$) (Fig. 5).

CLINICAL EVALUATION

Six of the eight patients reported noticeable improvement in symptoms of low cardiac output such as fatigue and weakness. Subjectively, dyspnoea decreased considerably in five and to a lesser degree in the remaining three patients. Examination disclosed that the extremities were warmer than in the period before prazosin. The intensity of the mitral regurgitation murmur decreased in seven patients.

Fig. 1 Peak effects of oral prazosin in patients with severe mitral regurgitation. Heart rate (left) was unchanged, while mean arterial pressure (right) declined significantly.

Fig. 2 At peak effect, oral prazosin increased cardiac index (left) and stroke volume (right) in each patient.

SIDE EFFECTS

No untoward effects were observed with administration of prazosin. None of the patients manifested hypotension, tachycardia, or evidence of myocardial ischaemia. No cardiac arrhythmias were observed. Overall, all patients tolerated single dose prazosin without any side effects.

Discussion

Systemic vascular resistance is one of the important determinants of left ventricular function.¹⁴ It has been shown that an increase in systemic vascular resistance may be detrimental, whereas a decrease may be beneficial in heart failure.^{15, 16} Most patients with heart failure also have an increase in blood volume (preload) which in the early stages of heart failure is a compensatory phenomenon to maintain cardiac output.⁴ Nevertheless, persistently raised preload may be detrimental to left ventricular performance because of increased heart size. In several studies^{9, 16-18} salutary effects of nitroprusside infusion in heart failure patients have been shown. These effects are thought to be related to a simultaneous decrease in both afterload and preload by nitroprusside. Load reduction therapy with nitroprusside also improves forward cardiac output and decreases regurgitant fraction in valvular regurgitant lesions.^{6, 7, 19} However, nitroprusside therapy is limited to patients in hospital because it has to be administered intravenously. Moreover, the haemodynamic effects of nitroprusside last only for the duration of the infusion.

The results of our study show that oral prazosin resulted in an improved haemodynamic response in patients with severe chronic mitral regurgitation and heart failure. Forward cardiac output and stroke volume increased. Simultaneously, a significant decline in pulmonary artery and left ventricular filling pressures occurred. These effects occurred in association with a distinct decrease in resistance in

Fig. 3 Oral prazosin administration resulted in a decline in mean pulmonary artery (left) and left ventricular filling pressures (right) in each patient.

both systemic and pulmonary vascular beds. In each patient with mitral regurgitation, the amplitude of the regurgitant "v" wave observed in the pulmonary wedge pressure tracing declined. Since heart rate and arterial pressure fell slightly, it is unlikely that the myocardial oxygen demands increased, while the left ventricular performance improved.

In this study, the haemodynamic effects of oral prazosin were first observed between 15 and 30 minutes after administration, peaked between 45 and 60 minutes, and persisted for six hours. These observations on the onset and duration of action are similar to those previously reported by us,^{9 20} and others.^{10 11}

The precise mechanism responsible for a vasodilator-associated increase in forward cardiac output in patients with valvular regurgitation lesions and heart failure is not known. It has been suggested that a decrease in systemic vascular resistance by

vasodilators results in improved forward cardiac output and reduced regurgitation fraction.^{6 7 19} Studies in our laboratory have shown that in patients with heart failure, the compliance of the aorta is decreased and the vascular load much increased.²¹ Preliminary studies suggest that nitroprusside improves cardiac output in patients with heart failure while both peripheral resistance and characteristic aortic impedance decline. The latter finding also implies an alteration of aortic distensibility.¹⁸ The present data in a small number of subjects show that indices of cardiac performance are improved by oral prazosin in patients with severe mitral regurgitation and heart failure. Though we did not directly measure the regurgitation fraction, the increases in stroke volume and stroke work index together with the reduced pulmonary capillary "v" wave suggest enhanced forward flow in association with a decrease in vascular load in these patients.

Fig. 5 At peak effect of prazosin, systemic (left) and pulmonary (right) vascular resistances were lower compared with the control state in each patient.

Fig. 4 Effects of prazosin administration on "v" wave in the pulmonary artery wedge pressure in a patient with severe mitral regurgitation. A decrease in "v" wave amplitude is seen at 15 minutes with further decline at 30 minutes.

The reduction in preload resulting from prazosin may be of considerable importance in patients with mitral regurgitation. It has been suggested that left ventricular volume is an important determinant of the severity of mitral regurgitation.²² A decrease in preload and subsequently in left ventricular volume may result in reduced valvular regurgitation, and may reduce myocardial ischaemia when present. In a study using a relatively selective afterload reducing agent, hydralazine, in patients with severe mitral regurgitation,⁸ an improvement was reported in forward cardiac output related to the afterload-reducing actions of hydralazine. The investigators, however, expressed concern about the absence of a decline in left ventricular volume with this agent. Though left ventricular volume measurements were not made in our patients during

treatment with prazosin, a pronounced decline in the left ventricular filling pressure at the peak effect of prazosin suggests a decreased venous return to the left heart, hence a decrease in left ventricular volume. Dilatation of the venous capacitance bed by prazosin¹¹ may complement its afterload-reducing effects in patients with severe mitral regurgitation.

A pronounced decrease in symptoms of fatigue and dyspnoea as reported by our patients is probably a manifestation of enhanced cardiac output and reduced pulmonary pressure. In addition, a decrease in intensity of the mitral regurgitation murmur suggests a decrease in regurgitant volume.

In summary, our study shows that in patients with severe mitral regurgitation and heart failure, components of left ventricular afterload (systemic vascular resistance) and preload (left ventricular filling pressure) decline after prazosin. These haemodynamic effects result in improved cardiac performance, that is increased forward cardiac output and reduced left ventricular filling pressure. Prazosin may be a potentially useful agent in patients with severe mitral regurgitation. Furthermore, absence of cardiostimulatory properties may make prazosin useful in patients with mitral regurgitation associated with ischaemic heart disease.

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