Effect of oral propranolol on rest and exercise left ventricular ejection fraction, volumes, and segmental wall motion in patients with angina pectoris

*Assessment with equilibrium gated blood pool imaging**

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SUMMARY The effect of oral propranolol on left ventricular ejection fraction, left ventricular volumes, cardiac output, and segmental wall motion was assessed with multigated blood pool imaging both at rest and during supine exercise in 15 patients with angina pectoris. Propranolol had no effect on resting left ventricular ejection fractions. Before propranolol, they did not change during exercise, whereas after propranolol the ejection fractions increased slightly. Exercise left ventricular ejection fractions increased with propranolol in three patients with resting left ventricular ejection fractions of <40 per cent.

More specifically, left ventricular end-diastolic volume index, end-systolic volume index, stroke volume index, and cardiac index were not altered significantly at rest or during exercise by propranolol. Exercise left ventricular ejection fractions were increased in five and unchanged in eight patients by propranolol. Those patients with increases in left ventricular ejection fractions had a greater change in left ventricular end-diastolic volume indices and a greater change in left ventricular end-systolic volume indices during exercise while on propranolol. Left ventricular segmental wall motion was not altered significantly during exercise by propranolol.

We conclude that: (1) Left ventricular functional responses to propranolol during exercise are heterogeneous and not easily predicted; (2) propranolol causes no consistent deterioration in exercise left ventricular ejection fraction even in patients with resting left ventricular ejection fractions <40 per cent; (3) increased exercise left ventricular ejection fraction with propranolol is contributed to by significant increases in end-diastolic volume during exercise; and (4) gated blood pool imaging is a useful method for characterising rest and exercise left ventricular ejection fractions and left ventricular volumes during propranolol therapy.

The beneficial effects of propranolol on exercise-induced myocardial ischaemia are well known.¹ The administration of propranolol inhibits the positive inotropic and chronotropic responses to local and circulating catecholamines, often resulting in less frequent angina pectoris and improved exercise tolerance. In some patients, however, left ventricular function may deteriorate with propranolol treatment resulting in congestive heart failure. Previous studies using the acute administration of intravenous propranolol in man

have failed to document a consistent negative effect on left ventricular function in the basal state.²⁻⁵ In addition, the effects of oral propranolol on myocardial function at rest have not been characterised completely.⁶⁻⁸ Since the effects of propranolol should be most pronounced during periods of sympathetic stimulation (such as exercise), and since the chronic oral effects of propranolol may be different from those produced by single dose intravenous treatment it seems important to evaluate the influence of chronic oral propranolol treatment on left ventricular function both at rest and during exercise. Several preliminary reports and one recent detailed communication have sug-

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gested that oral propranolol improves left ventricular ejection fraction during exercise in patients with coronary artery disease.⁸⁻¹⁰ The present study was performed to assess the effects of oral propranolol on resting and exercising left ventricular performance in individuals with angina pectoris, using the technique of multigated equilibrium blood pool imaging. We specifically wished to determine whether: (1) chronic oral propranolol treatment increases left ventricular ejection fraction during exercise; (2) propranolol administration has any consistent beneficial or detrimental effect on left ventricular volumes that might not be apparent if only left ventricular ejection fraction is analysed; and (3) whether there are identifiable patient subgroups that have different left ventricular functional responses to propranolol during exercise.

Patients and methods

PATIENT POPULATION

The study population consisted of 15 patients with angina pectoris (13 male and 2 female) with a mean age of 56.4 years (range, 39 to 73 years) (Table 1). In all patients propranolol treatment was instituted for the treatment of angina pectoris.

Table 1 Patient data

Case No.	Age (y)	Sex	Maximum propranolol dose/day (mg)	Peak workload (kpm)	
				Baseline	Propranolol
1	73	M	400	150	300
2	66	F	160	300	300
3	40	M	160	450	600
4	61	M	80	450	300
5	65	M	80	450	450
6	39	M	60	150	150
7	53	M	320	300	600
8	57	M	120	150	150
9	62	M	80	150	300
10	61	M	320	150	150
11	64	M	80	150	150
12	68	M	160	150	150
13	40	M	160	600	600
14	53	M	80	150	150
15	44	F	160	300	300

The diagnosis of coronary artery disease was based on a history of angina pectoris and: (1) the angiographic demonstration of coronary artery narrowing equal to or greater than a 70 per cent decrease in luminal diameter (10 patients), and/or (2) an abnormal exercise tolerance test demonstrating 1 mm or greater horizontal or downsloping ST segment depression of a least 0.08 s duration in a lead with a normal resting tracing (five patients). In the 10 patients undergoing coronary arteriography, four had significant narrowing of three major coronary

arteries, three had involvement of two vessels, and three had single vessel disease. One patient had previous coronary artery bypass grafting with the angiographic demonstration of graft closure in one of three grafts and an abnormal exercise tolerance test. Twelve patients developed chest pain and ST segment depression during the baseline study while three had non-diagnostic tests. During propranolol treatment nine patients continued to manifest chest pain and ST segment changes, the remaining patients having non-diagnostic electrocardiographic changes. Seven patients had previous well documented myocardial infarctions. None of the patients had evidence of mitral valve prolapse. Three patients had earlier clinical evidence of congestive heart failure and were being treated with digitalis and/or diuretics during the study period. None of these patients had evidence of congestive heart failure, either clinical or radiological, at the time of the study. In the three patients taking digoxin, the presence of coronary artery disease was documented by arteriography.

EXERCISE TEST PROCEDURE

Exercise testing was conducted in the supine position with a bicycle ergometer (Engineering Dynamics Corporation—Lowell, Mass.) during continuous electrocardiographic monitoring with an orthogonal lead system. Graded exercise was performed for four minutes at each work load beginning at 150 kpm (kilopond metres) and continuing in increments of 150 kpm until one of the following end-points was reached: (1) patient fatigue, (2) typical anginal chest pain, (3) an abnormal electrocardiographic response, or (4) significant ventricular arrhythmias. All tests were performed in the fasting state. Repeat exercise tests after the institution of oral propranolol were performed approximately three to four hours after a dose of propranolol and only after a minimum of three days at a stable dosage schedule. In all but one patient an equivalent or greater workload was achieved on propranolol (Table 1).

DRUG ADMINISTRATION PROCEDURE

After the baseline studies, oral propranolol treatment was instituted at 40 to 80 mg/day administered as four equal doses every six hours. Dosages were increased in a stepwise fashion until the clinician caring for the patient believed the patient was receiving the maximal dose that was advisable. The mean propranolol dosage was 161 mg/day (range 60 mg to 400 mg) (Table 1). No patient had ischaemic chest pain or had taken glyceryl trinitrate during the four hours before the exercise studies and none showed an important change in clinical

symptoms or physical examination between the two exercise studies.

RADIONUCLIDE TECHNIQUES AND IMAGING PROCEDURE

Multigated equilibrium blood pool imaging was performed using in vivo labelling of red blood cells with unlabelled stannous pyrophosphate (New England Nuclear—Pyrolite) before 30 mCi of ^{99m}Tc as sodium pertechnetate.^{11 12} Collection of data was performed with a standard gamma scintillation camera (Ohio Nuclear Series 100) equipped with an all purpose parallel hole collimator and interfaced with a dedicated on-line computer system (Ohio Nuclear VIP-450). Resting equilibrium gated blood pool scintigrams were obtained in multiple projections including a 35° LAO projection modified to include a 15° caudad angulation of the collimator surface. Though this projection frequently separates the right from left ventricle, the angle of obliquity was always adjusted to allow the clearest separation between the ventricles while minimising the interventricular septal thickness. Resting studies were acquired for: (1) a preselected time interval (five to eight min), (2) 28 frames per cardiac cycle, and (3) 90 to 100 per cent of the cardiac cycle. This resulted in a minimum of 200 000 counts per frame of the study.

Before beginning the exercise study, the legs of the patients were raised into the bicycle pedals and, after allowing two minutes for equilibration, an additional resting scintigram was obtained. This was done to assess the effect of leg elevation alone on the indices of left ventricular function. These and all subsequent exercise scintigrams were acquired for: (1) a preselected time interval of three minutes, (2) 24 frames per cardiac cycle, and (3) 90 to 100 per cent of the cardiac cycle. This resulted in a minimum of 100 000 counts per frame of the study. Exercise imaging was performed at each work load, beginning at 150 kpm and continuing until the termination of the test. The work levels achieved during the baseline study and after propranolol treatment are shown in Table 1. At the beginning of the first and each subsequent work load, the patient exercised for one minute before beginning the three minute imaging period. This allowed the heart rate to attain levels that were consistent enough to allow gating to proceed smoothly.

CALCULATION OF SCINTIGRAPHIC LEFT VENTRICULAR EJECTION FRACTION AND VOLUMES

Left ventricular ejection fractions were determined from the time activity curve of the left ventricle by constructing a region of interest over the left

ventricle in the frames corresponding to end-diastole (ED) and end-systole (ES). The number of counts within the region of interest was used to calculate the left ventricular ejection fraction using the formula:

$$\text{LVEF} = \frac{\text{Background corrected ED counts} - \text{background corrected ES counts}}{\text{background corrected ED counts}}$$

This method has been shown to correlate well with results obtained by contrast ventriculography.¹³

Left ventricular volumes were estimated by a non-geometric technique recently developed and validated in our laboratory.¹⁴⁻¹⁶ Further support for this technique comes from the independent work of Slutsky *et al.*¹⁷ In brief, the end-diastolic and end-systolic frames were isolated from the multiframe gated study and used for further processing. Correction for background activity was performed using a linear interpolated background subtraction technique which provided a highly reproducible and objective assessment of background activity.¹⁶ A region of interest was constructed over the left ventricle at end-diastole and end-systole, cautiously excluding left atrial activity and adhering to consistent criteria for the definition of the ventricular borders. Scintigraphic estimates of left ventricular volumes were calculated from the activity of the left ventricular region of interest normalised for heart rate, acquisition time per frame, and activity per millilitre of peripheral venous blood. The following equation was used for the scintigraphic estimation of left ventricular volumes:

$$\text{Volume} = \frac{\frac{\text{Background corrected LV counts}}{\% \text{ cycle acquired}}}{\frac{\text{No. of frames gated}}{\text{Peripheral blood activity} \times e^{-\lambda t}}} \times T_{\text{total}}$$

where $e^{-\lambda t}$ is the general equation for isotope decay ($\lambda = 0.693/\text{isotope half-life}$) and T_{total} is the total acquisition time of the study. Because of chest wall attenuation, the scintigraphic estimates of ventricular volumes are consistently smaller than the angiographic ones. Hence, a regression equation was determined (angiographic volume = $4.98 \times$ scintigraphic volume estimate + 6.91), and the results of the volume determinations expressed in terms of the regressed angiographic volume estimate. Since the y-intercept of the regression equation is not zero, back calculation of the left ventricular ejection fraction from the scintigraphically determined volumes differs slightly from the count-derived ejection fractions that are reported. Using this method, we have found

excellent correlations ($r=0.95$) between scintigraphic and angiographic left ventricular volume measurements.¹⁶ Using these left ventricular volume measurements, stroke volume and cardiac output were also derived.

A subjective analysis of left ventricular segmental wall motion was also obtained. The left ventricle was divided into five segments, and each segment graded according to the following scale: 3 = normokinesis, 2 = mild hypokinesis, 1 = severe hypokinesis, 0 = akinesis, and -1 = dyskinesis. Further breakdown of this grading scheme was allowed, hence, a score of 1.5 would indicate left ventricular segmental wall motion between mild and severe hypokinesis.

STATISTICAL ANALYSIS

Data are expressed as the mean $\pm$ (SD). Comparisons between radionuclide studies in individuals were made by the paired *t* test, and comparisons between groups were performed with an unpaired *t* test. Values were considered statistically significant when a two tailed *t* test identified *p* values of less than 0.05.

Results

Ten of the 15 patients treated with propranolol showed improvement in their exercise tolerance tests, as manifested by either less chest pain at equivalent work loads, less ST segment depression with exercise at equivalent work loads, and/or an increased exercise capacity before the onset of

symptoms or ST segment changes. In this group, four patients were able to increase their work capacity by one work level while on propranolol treatment (Table 1). Four of the 15 patients experienced no improvement in exercise tolerance or chest pain while on propranolol, and one patient had slight deterioration in exercise capacity (less work performed) without clinical evidence of congestive heart failure. In addition, one patient developed intolerance to propranolol, manifest by excessive fatigue, which resolved after discontinuation of the drug. In the seven patients with previous infarction there was good agreement between the location of resting wall motion abnormalities and the site of previous infarction. Left ventricular functional indices before and after propranolol were compared at the highest equivalent work level achieved during both examinations.

HEART RATE AND DOUBLE PRODUCT

Both resting and peak exercise heart rates were lower while on propranolol (Tables 2 and 3). Mean resting heart rates before and after propranolol were 79 ± 10 beats/min and 65 ± 10 beats/min, respectively. Mean peak exercise heart rate was 113 ± 15 beats/min before treatment and 97 ± 12 beats/min after propranolol. Both differences were statistically significant ($p < 0.01$). The mean resting double product was lower after propranolol ($105 \pm 24 \times 10^2$ vs $81 \pm 15 \times 10^2$) ($p < 0.01$), as was the mean peak exercise double product ($185 \pm 62 \times 10^2$ vs $148 \pm 30 \times 10^2$) ($p < 0.02$). Four patients showed no blunting of exercise heart rate response during propranolol; nevertheless, three of these

Table 2 Baseline exercise test. Responses of left ventricular volumes and left ventricular ejection fraction to exercise during the baseline (pretreatment) exercise tolerance test

Case No.	EDVI (ml/m ²)		ESVI (ml/m ²)		SVI (ml/m ²)		CI (l/min per m ²)		EF		HR		DP $\times 10^2$	
	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
1	83	102	32	43	51	59	3.8	5.9	0.65	0.60	74	100	126	180
2	38	47	7	13	31	34	2.9	4.9	0.80	0.73	93	147	155	353
3	41	48	14	13	27	36	1.9	4.5	0.72	0.79	70	125	91	200
4	95	98	48	36	57	61	3.0	6.0	0.52	0.65	62	98	67	118
5	85	89	31	27	55	62	3.7	6.5	0.67	0.73	68	105	85	173
6	137	132	102	107	35	25	3.2	2.7	0.27	0.20	91	114	82	114
7	68	84	21	31	47	54	3.7	5.2	0.72	0.66	78	96	105	163
8	59	87	21	33	39	44	2.9	6.1	0.69	0.64	63	112	82	190
9	96	127	40	47	57	80	4.1	8.0	0.61	0.65	73	108	91	162
10	54	55	27	25	28	30	2.4	3.4	0.55	0.58	90	114	113	182
11	135	146	86	88	50	58	4.0	6.2	0.38	0.41	80	106	96	127
12	47	56	11	11	36	44	3.0	4.9	0.83	0.85	84	110	118	154
13	90	95	45	22	45	73	4.0	10.3	0.52	0.80	88	142	123	284
14	91	111	61	74	31	37	2.3	3.8	0.35	0.34	74	105	89	168
15	77	100	29	22	48	78	4.3	8.6	0.67	0.82	90	110	135	209
Mean	80	92	38	39	42	52	3.3	5.8	0.60	0.63	79	113	105	185
SD	± 29.2	± 29.1	± 26.2	± 28.4	± 10.6	± 17.6	± 0.76	± 2.04	± 0.16	± 0.18	± 10	± 15	± 24	± 62

R, resting; Ex, exercise; EDV, LV end-diastolic volume; ESV, LV end-systolic volume; SV, stroke volume; CI, cardiac index; EF, LV ejection fraction; HR, heart rate; DP, double product (systolic blood pressure $\times$ heart rate).

Table 3 Propranolol exercise test. Responses of left ventricular volumes and left ventricular ejection fractions to exercise during propranolol treatment

Case No.	EDVI (ml/m ²)		ESVI (ml/m ²)		SVI (ml/m ²)		CI (l/min per m ²)		EF		HR		DP × 10 ²	
	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex	R	Ex
1	55	95	23	37	32	58	1.7	4.4	0.63	0.63	53	76	69	196
2	62	96	13	11	48	86	2.6	7.1	0.84	0.93	52	83	68	149
3	49	53	12	14	37	39	2.8	4.0	0.82	0.79	76	102	95	168
4	90	99	36	28	54	71	3.9	7.1	0.62	0.74	73	100	73	130
5	85	87	26	22	58	66	3.2	6.9	0.72	0.78	55	105	66	168
6	154	200	121	147	33	52	2.4	5.6	0.22	0.27	74	106	70	127
7	66	84	20	24	46	60	2.4	5.1	0.73	0.74	52	85	62	119
8	48	61	16	17	32	44	1.8	3.9	0.71	0.66	56	88	78	136
9	116	134	57	65	59	69	3.6	6.6	0.53	0.53	61	112	79	144
10	85	84	47	44	38	40	2.4	3.7	0.47	0.50	64	93	83	139
11	127	153	84	85	42	68	3.5	7.1	0.35	0.46	82	105	90	122
12	69	66	16	15	53	50	3.6	4.3	0.82	0.81	68	85	122	144
13	93	114	35	35	58	70	4.2	9.4	0.65	0.71	73	120	95	230
14	96	103	57	63	39	41	3.0	4.0	0.43	0.41	76	98	95	147
15	86	91	30	22	56	69	3.1	6.4	0.69	0.80	56	92	84	156
Mean	85	101	39	42	46	59	3.0	5.7	0.61	0.65	65	97	81	148
SD	± 29.3	± 38.4	± 29.1	± 35.1	± 10.5	± 14.6	± 0.75	± 1.68	± 0.18	± 0.18	± 10	± 12	± 15	± 30

Abbreviations are the same as in Table 2.

four did show an improvement in left ventricular ejection fraction.

LV END-DIASTOLIC AND END-SYSTOLIC VOLUMES

Mean resting end-diastolic volume index did not change with propranolol (80 ± 29.2 ml/m² before propranolol, 85 ± 29.3 ml/m² after propranolol) (Fig. 1) (Tables 2 and 3). Similarly, peak exercise left ventricular end-diastolic volume index did not change significantly (92 ± 29.1 ml/m² before propranolol, 101 ± 38.4 ml/m² after propranolol).

Left ventricular end-diastolic volume index, however, did increase significantly ($p < 0.01$) with exercise both before and after propranolol treatment. Before treatment, the mean rise with exercise was 17 ± 13 per cent, and after propranolol the mean rise with exercise was 20 ± 20 per cent. There was no correlation ($r < 0.5$) between the magnitude of reduction in resting heart rate and the degree of increase in resting left ventricular end-diastolic volume index with propranolol.

Mean resting left ventricular end-systolic volume index did not change before (38 ± 26.2 ml/m²) or after (39 ± 29.1 ml/m²) propranolol (Fig. 2) (Tables 2 and 3). Similarly, mean peak exercise left ventricular end-systolic volume indices did not change during propranolol (39 ± 28.4 ml/m² before and 42 ± 35.1 ml/m² during propranolol). In addition, there was no significant change in left ventricular end-systolic volume index with exercise either before or after propranolol.

STROKE VOLUME AND CARDIAC OUTPUT

The mean resting stroke volume index before

Fig. 1 The effects of propranolol on resting and peak-exercise end-diastolic volume is shown. The pretreatment study in this and subsequent figures is indicated as the baseline study. Mean values ($\pm$ SD) are displayed to the side of the individual patient values. Though no significant changes were noted in left ventricular end-diastolic volume indices on propranolol treatment, conspicuous individual variation is shown.

propranolol was 42 ± 10.6 ml/m², whereas after propranolol it was 46 ± 10.5 ml/m² (NS) (Fig. 3) (Tables 2 and 3). Mean peak exercise stroke volume indices were similar before and during propranolol (52 ± 17.6 ml/m² before and 59 ± 14.6 ml/m² during propranolol) (NS). There was a significant increase in stroke volume index with exercise in both groups. Before propranolol, stroke volume index rose by 10 ± 10.3 ml/m² with exercise,

Fig. 2 Effect of propranolol on rest and exercise end-systolic volume. No substantial alterations in left ventricular end-systolic volume indices were seen before or after propranolol treatment. The format is identical to that in previous figures.

Fig. 3 Effect of propranolol on rest and exercise stroke volume. The format is as in previous figures. No consistent effect on stroke volume index was found.

whereas during propranolol treatment, stroke volume index rose by 14 ± 11.1 ml/m² with exercise.

The mean resting cardiac index was not different before or after propranolol (3.3 ± 0.76 l/min per m² and 3.0 ± 0.75 l/min per m², respectively), nor was the cardiac index at peak exercise (5.8 ± 2.04 l/min per m² before and 5.7 ± 1.68 l/min per m² after the drug) (Fig. 4) (Tables 2 and 3). Cardiac index, however, rose significantly ($p < 0.001$) with exercise, and this rise was not altered by propranolol (2.6 ± 1.58 l/min per m² before and 2.7 ± 1.31 l/min per m² after propranolol).

Fig. 4 Effect of propranolol on rest and exercise cardiac index. The format is as in previous figures. Though cardiac index increased with exercise in both groups, no effect of propranolol was seen.

LEFT VENTRICULAR EJECTION FRACTION

The mean resting left ventricular ejection fraction before propranolol was 0.60 ± 0.16 , and after propranolol it was 0.61 ± 0.18 (NS) (Fig. 5). The mean peak exercise left ventricular ejection fraction was not different before or after propranolol treatment, 0.63 ± 0.18 vs 0.65 ± 0.18 , respectively. Before propranolol treatment, there was no significant rise in mean left ventricular ejection fraction with exercise. After propranolol, however, mean left ventricular ejection fraction rose from 0.61 ± 0.18 to 0.65 ± 0.18 with exercise, a difference which, though small, was statistically significant ($p < 0.05$).

Data regarding interobserver, intraobserver, and individual patient variability suggest, however, that an absolute change in left ventricular ejection fraction of 0.05 or greater should be present to consider a change in left ventricular ejection fraction significant.¹⁷ Applying this criterion to the individual patient data, the response of the left ventricular ejection fraction to exercise before and after propranolol treatment can be recategorised (Fig. 6). Before propranolol, left ventricular ejection fraction increased with exercise in five of the 15 patients (33%), was unchanged in five of the 15 (33%), and deteriorated in five of the 15 (33%). After propranolol, left ventricular ejection fraction improved with exercise in seven of the 15 patients (47%), remained unchanged in seven of the 15 (47%), and deteriorated in only one of the 15 patients (6%) (Fig. 6). Fig. 6 also shows that five patients had an improved response in left ventricular ejection fraction from rest to exercise after propranolol, whereas in nine patients the left ventricular ejection fractions showed the same response to exercise before and after propranolol. The one patient

Fig. 5 Effect of propranolol on rest and exercise left ventricular ejection fraction. No significant change in resting ejection fraction was observed; however, after propranolol there was a small but statistically significant increase in left ventricular ejection fraction with exercise. Considerable individual variation in the magnitude and direction of the response of exercise left ventricular ejection fraction to propranolol is also shown.

(case 8) with a fall in exercise left ventricular ejection fraction before and after propranolol was subsequently shown to have severe (>95%) stenosis of the left main coronary artery. The

response of left ventricular ejection fraction to exercise in one patient (case 3) was worse during propranolol treatment when the comparison was made at the highest work level achieved before treatment (Tables 2 and 3). During propranolol treatment, however, this patient performed to the next highest work level, with a further increase in left ventricular ejection fraction to 0.87, allowing him to be recategorised into the improved response group. Thus, in most patients exercise left ventricular ejection fractions were either improved or unchanged by propranolol.

In order to assess further the improved exercise left ventricular ejection fractions after propranolol in five of the patients, the exercise induced changes in left ventricular volumes were compared with those in eight patients in whom exercise left ventricular ejection fractions were unchanged during propranolol (Table 4). The patient with left main coronary stenosis and the patient with a similar left ventricular ejection fraction response but at nonequivalent workloads were excluded from this analysis, since each may represent a special circumstance. Before propranolol, there was no difference in the mean change in left ventricular end-diastolic or end-systolic volume index with exercise between the two groups (Table 4). After propranolol, however, the mean change in left ventricular end-diastolic volume indices was larger in the

Fig. 6 Response of left ventricular ejection fraction to exercise before and after propranolol treatment. Each solid line represents the change in the response of exercise left ventricular ejection fraction during propranolol treatment in an individual patient. In five patients, the left ventricular ejection fractions during exercise were improved during propranolol treatment. One patient (case 3) had a poorer performance on propranolol (class ↓ to class O) when the comparison was made at the highest work level achieved before propranolol. This same patient, however, exercised to a higher work level during propranolol treatment resulting in a further increase in left ventricular ejection fraction. This allowed the patient to be reclassified into a different response group (dashed line).

Exercise LV function during propranolol

Table 4 Exercise tolerance test. Changes in end-diastolic volume index and end-systolic volume index (EDVI) (ESVI) during exercise in five patients with an improved left ventricular ejection fraction response on propranolol and in eight patients with the same left ventricular ejection fraction response during propranolol treatment

Patient Group	Baseline Δ EDVI with exercise ml/m ²	Propranolol Δ EDVI with exercise ml/m ²
Improved LVEF with propranolol N = 5	9 $\pm$ 8.9	33 $\pm$ 11.1 (p < 0.001)
Unchanged LVEF with propranolol N = 8	14 $\pm$ 11.5	6 $\pm$ 7.1
	Δ ESVI with exercise	Δ ESVI with exercise
Improved LVEF with propranolol N = 5	7 $\pm$ 3.7	10 $\pm$ 10.4 (p < 0.025)
Unchanged LVEF with propranolol N = 8	1 $\pm$ 8.7	- 1 $\pm$ 5.8

Abbreviations: Baseline, prepropranolol; Δ EDVI, change in LV end-diastolic volume index; Δ ESVI, change in LV end-systolic volume index.

group with improved left ventricular ejection fractions compared with the patients with unchanged ejection fractions (33 $\pm$ 11.1 ml/m² vs 6 $\pm$ 7.1 ml/m², respectively; p < 0.001). It is unlikely that this was the result solely of alterations in heart rate, since the mean peak heart rates were equivalent in both groups (91 $\pm$ 13.6 improved group vs 97 $\pm$ 9.0 unchanged group) [NS]. In addition, the magnitude of change in heart rate from rest to exercise, was similar. Similarly after propranolol, the mean change in left ventricular end-systolic volume indices with exercise was larger (10 $\pm$ 10.4 ml/m² vs -1 $\pm$ 5.8 ml/m², p < 0.025) in the group with an improved exercise left ventricular ejection fraction response compared with those with unchanged left ventricular ejection fraction responses during exercise.

Four patients increased their exercise capacity after propranolol resulting in a further increase in double product. Two of these four reached the equivalent double product of the pretreatment exercise test, whereas in the remaining two, the double product remained diminished (Tables 2 and 3). Only one of these four (case 3) had a substantial increase in left ventricular ejection fraction with the increased workload.

WALL MOTION ANALYSIS

In the 15 patients, there was a total of 75 left ventricular wall segments available for evaluation (five segments/patient). The imaging projection used does not allow visualisation of all wall seg-

ments, hence abnormalities in the anterior and inferoposterior regions will not be visualised directly. None the less, the development of abnormalities in these areas during exercise has the potential for effecting global left ventricular function and thus could be detected indirectly by alterations in left ventricular ejection fraction. In the seven patients with previous myocardial infarcts there was good agreement between the location of infarction and the location of resting wall motion abnormalities. Analysis of resting wall motion before propranolol indicated 18 of 75 segments (24%) to be hypokinetic and six (8%) to be akinetic. Seventy-nine per cent of these abnormal segments were in areas of previous infarction. After propranolol, 22 of 75 segments (29%) were hypokinetic and seven of 75 (9%) were akinetic. Overall, 14 of 75 segments (18.6%) had less motion during propranolol, seven segments developing new mild changes ($\leq$ 1 unit) in areas that were previously normal and seven showing more severe changes in areas already abnormal. Ten of 75 segments (13.3) showed improved wall motion after propranolol.

Analysis of exercise left ventricular wall motion before propranolol showed 26 of 75 segments (34.6%) to be hypokinetic and five of 75 (6.7%) to be akinetic. After propranolol 23 of 75 segments (30.7%) were hypokinetic at exercise and eight of 75 (10.7%) were akinetic. Overall, 13 segments (17.3%) were more hypokinetic on propranolol and 11 (14.7%) were less hypokinetic.

Discussion

Propranolol is currently the major beta-blocker used in the treatment of patients with angina pectoris. Since it is so frequently used, it is important that its effect on left ventricular function is characterised thoroughly both at rest and during exercise. This study was performed to assess the effect of oral propranolol on rest and exercise left ventricular end-diastolic and end-systolic volumes, stroke volume, cardiac output, and ejection fraction, all assessed during supine exercise with multigated equilibrium blood pool imaging. Recent developments with this radionuclide technique have shown it to be a reliable and reproducible method for the measurement of these indices of left ventricular function and segmental wall motion.¹³⁻²²

In the patients studied, propranolol resulted in lower resting and exercise heart rates and double products. In addition, propranolol administration was associated with substantial improvement in exercise induced angina and/or work performance in most patients. These observations show that the

study population received a substantial dose of propranolol.

Left ventricular ejection fraction is the most commonly used clinical index to assess global left ventricular function in patients. In the present study propranolol caused no change in resting global left ventricular ejection fractions, confirming the studies of Marshall *et al.*⁷ and Battler *et al.*⁸ who have reported similar results using radio-nuclide techniques. Previous studies using echocardiographic techniques have shown either no change²³ or a reduction⁶ in resting left ventricular ejection fraction with oral propranolol treatment. This discrepancy may, in part, be the result of the well recognised limitations of single dimension echocardiographic analysis in patients with segmental wall motion abnormalities.²⁴ Though peak exercise left ventricular ejection fractions were not different on propranolol, there was a small (but significantly greater) increase in left ventricular ejection fractions from rest to exercise in the propranolol treated group. Further analysis of the individual patient responses to exercise before and after propranolol indicated no new deterioration in left ventricular ejection fractions with propranolol administration, even in the patients with resting ejection fractions less than 40 per cent before propranolol. Moreover, an increase in exercise left ventricular ejection fractions during propranolol was seen in one-third of the patients studied. Recent reports have indicated that oral propranolol causes substantial improvement in exercise left ventricular ejection fractions in patients with coronary artery disease.⁸⁻¹⁰ In a study of 10 patients with ischaemic heart disease, Battler *et al.*⁸ concluded that the average left ventricular ejection fraction increased by 22 per cent relative to the value during the same exercise but without propranolol. Though our results indicate a statistically significant improvement in exercise left ventricular ejection fractions on propranolol, the increases were not as dramatic. In addition, our data suggest substantial individual variation in the exercise response of left ventricular ejection fraction to propranolol.

The scintigraphic estimation of left ventricular volumes in the patients studied helps to clarify the reason for at least part of this variation. Patients with an improvement in exercise left ventricular ejection fractions after propranolol had a significantly greater increase in left ventricular end-diastolic volume indices with exercise while on propranolol. In addition, in this subset of patients, there was a small but significant increase in left ventricular end-systolic volume indices with exercise during propranolol. These alterations in left ventricular volumes were not detectable in the

subset of patients in whom similar changes in left ventricular ejection fractions occurred before and after propranolol treatment. Hence, improvement in left ventricular ejection fractions with propranolol appear to be associated with increases in left ventricular end-diastolic volumes during exercise. It is unlikely that these alterations in left ventricular end-diastolic volumes are secondary to alterations in heart rate alone, since both exercise heart rates and the change in heart rates with exercise were not significantly different in the two groups studied. The reason(s) for the alterations in left ventricular end-diastolic volumes is not clear, but it may have been related at least in part to altered left ventricular compliance.

Left ventricular end-systolic volume indices were not significantly changed during exercise or by propranolol in the study population as a whole; they, however, increased slightly during exercise in the subset of patients showing improvements in left ventricular ejection fractions after propranolol. Grossman *et al.*²⁵ have shown that the contractile state of the left ventricle may be evaluated using end-systolic pressure-volume relations. If end-systolic volume serves as an index of contractility, it is not surprising that beta-blockade caused no change in resting end-systolic volume, since beta-adrenergic support of the left ventricle is small in the basal state. Previous investigations have shown a fall in left ventricular end-systolic volume during exercise in normal subjects.²⁶⁻²⁸ Our data obtained in patients with angina pectoris indicate that left ventricular end-systolic volume index does not change with exercise. This may be an additional manifestation of ischaemia and one indicating that contractility has been affected adversely. Sonnenblick *et al.*²⁹ have shown that propranolol prevents an increase in contractility normally associated with exercise. This effect was possibly shown in the five patients who manifested an increase in exercise left ventricular end-systolic volumes after propranolol.

Three of the patients we studied had resting left ventricular ejection fractions of less than 40 per cent. During exercise, each of these patients showed a higher left ventricular ejection fraction while on propranolol, whereas at rest left ventricular ejection fractions were slightly lower in two of the three during propranolol treatment.

Resting and exercise left ventricular stroke volume indices were not different after propranolol; there was, however, prominent individual variability. This finding is in agreement with angiographic data obtained after the acute administration of intravenous propranolol.³⁻⁵ In the patients we studied, cardiac indices were not altered by pro-

pranolol treatment at rest or during exercise. Exercise cardiac indices also disclosed a conspicuous degree of individual variation (Table 2, Fig. 3).

Subjective analysis of left ventricular wall motion also showed a heterogeneous response to propranolol treatment. Most left ventricular wall segments (approximately 68%) remained unchanged during propranolol both at rest and during exercise. However, 18 per cent of the segments became more hypokinetic, whereas 14 per cent were less hypokinetic during propranolol. Previous reports of the effects of propranolol on left ventricular wall motion are conflicting.^{2 4 5 23 30} Many of these previous investigations used intravenous propranolol; hence, the extrapolation of these data to those obtained with chronic oral treatment is unclear. While some previous studies have shown new or worsening areas of asynergy,⁵ others have failed to show any impairment in segmental left ventricular function.² Non-invasive studies of the effect of chronic oral propranolol on left ventricular function are also conflicting.^{6 31} During experimental myocardial ischaemia, however, beta-adrenergic blockade has been shown to improve acutely regional left ventricular function, presumably by decreasing oxygen demand.³²⁻³⁴

In summary, the data obtained in the present study emphasise that the exercise response of left ventricular function to propranolol in patients with angina pectoris is complex and not entirely predictable. Propranolol resulted in either improved or unchanged left ventricular ejection fractions during exercise when compared with baseline responses, and notably did not result in a detrimental effect in patients with resting left ventricular ejection fractions less than 40 per cent. The mechanisms responsible for the increased left ventricular ejection fractions in a subset of patients are not clear but may be related in part to larger changes in left ventricular end-diastolic volumes during exercise. These functional alterations to propranolol, however, have been established during supine bicycle exercise and whether similar changes occur during upright exercise is unknown. Since the overall supine exercise left ventricular functional response to propranolol is heterogeneous, it may be advisable to obtain functional testing before and during exercise in selected patients to determine whether left ventricular function is beneficially altered. The radionuclide methods used in this study seem particularly well suited to allow such evaluation, since they permit rapid and relatively non-invasive measurement of left ventricular ejection fraction, left ventricular volumes, and presently at least a subjective analysis of left ventricular segmental wall motion.

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