Effect of beta adrenergic blockade on thallium-201 myocardial perfusion imaging

B HOCKINGS,* S SALTISSE,† D N CROFT, M M WEBB-PEPLOE

From the Departments of Nuclear Medicine and Cardiology, St Thomas's Hospital, London

SUMMARY Nine patients with stable angina (group 1) underwent maximal treadmill stress testing and thallium-201 (^{201}Tl) myocardial scintigraphy after intravenous propranolol hydrochloride, and after placebo. Though seven of the nine patients exercised longer after propranolol than after placebo, this difference did not reach statistical significance. Propranolol, however, significantly reduced the mean maximum rate pressure product. Comparison of the perfusion scans on and off propranolol showed that in 36 out of 90 of the myocardial segments recorded (nine patients, five segments scanned twice per patient), only one of the scans showed a defect. In 24 out of 36 of these the propranolol scan was negative, the defect appearing in the placebo scan. Defects present on both scans but differing significantly in size occurred in 22 out of 54 view pairs (nine patients, three views after exercise and three views after redistribution on propranolol and on placebo), and in 19 of these the smaller defect was seen in the propranolol scan. In one of the nine patients, the propranolol scan was normal (false negative), whereas defects corresponding to angiographically proven coronary artery lesions were seen on the placebo scan.

Six patients (group 2) were maximally exercised after propranolol and then re-exercised to the same rate pressure product on placebo. Again 16 out of 60 of the segment pairs disagreed and in 10 of these the unmatched defect was present on the placebo scan. In 10 out of 14 discrepant view pairs, the smaller defect occurred on the propranolol scan. Thus in patients taking propranolol, negative results do not exclude coronary artery disease, and perfusion defects (if present) though accurately reflecting the presence of disease may underestimate its true extent.

The majority of patients undergoing ^{201}Tl thallium myocardial perfusion imaging have actual or suspected ischaemic heart disease and many are therefore being treated with beta adrenergic blocking agents. Recent tissue sampling on dogs without coronary artery disease has suggested that propranolol may decrease myocardial uptake of ^{201}Tl by 11 to 32%,^{1,2} though other workers have not found this.³ Despite the large numbers of patients taking beta blockers who undergo ^{201}Tl scanning, there are no reports of the effects of these drugs on myocardial perfusion as represented by the ^{201}Tl images in human subjects with coronary artery disease.

The aims of this study are threefold: (1) to investigate the effects of propranolol on the distribution of ^{201}Tl in the myocardium of patients with ischaemic disease as determined by external imaging. (2) To

investigate if such effects are related to changes in exercise capacity induced by the drug. (3) To determine whether ^{201}Tl scanning is best performed with the patient taking propranolol or after its temporary discontinuation.

Patients and methods

Twelve patients with stable angina pectoris were studied. The patients were all men, aged 36 to 58 years (mean 49.2 ± 7.3 years) (Table 1). Coronary arteriography (including both craniocaudal views) had shown a critical stenosis greater than 50% reduction in luminal diameter in at least one major coronary artery in every case. The treadmill stress tests and ^{201}Tl myocardial imaging were performed within six weeks of coronary arteriography. Six of the 12 subjects had a history of myocardial infarction, and one had undergone saphenous vein bypass grafting of the right coronary artery (Table 1). There were no other cardiac abnormalities.

*Present address: Royal Perth Hospital, Perth, Australia.

†Present address: North Tees General Hospital, Stockton-on-Tees, Cleveland.

Table 1 Clinical details and stress testing data on 12 male patients

Case No.	Age (y)	Previous MI	Format of exercise	Intervention	Duration of exercise (min)	Max RPP (beats/min per mmHg)
1	42	—	Max	Propranolol	8.0	12 413
			Max	Placebo	4.0	14 700
2	52	Anterior	Max	Propranolol	8.0	6333
			Max	Placebo	7.5	7467
3	57	Inferior	Max	Placebo	5.25	17 333
			Max	Propranolol	6.5	11 760
4	43	Inferior	Max	Propranolol	9.25	14 933
			Max	Placebo	7.75	15 817
5	58	Infero-posterior	Max	Propranolol	10.0	11 700
			Max	Placebo	11.0	16 500
6	56	—	Max	Propranolol	7.5	10 667
			Max	Placebo	7.0	13 920
7	38	Antero-septal	Max	Placebo	11.5	10 250
			Max	Propranolol	12.0	11 049
			SRPP	Placebo	10.75	10 620
8	48	—	Max	Propranolol	13.0	11 917
			Max	Placebo	8.5	13 125
			SRPP	Placebo	7.0	12 200
9	57	—	Max	Propranolol	6.0	9270
			Max	Placebo	9.0	16 560
			SRPP	Placebo	6.0	9900
10	44	—	Max	Propranolol	10.0	9440
			SRPP	Placebo	7.0	9920
11	36	—	Max	Propranolol	7.25	10 815
			SRPP	Placebo	6.5	10 476
12	45	Inferior	Max	Propranolol	5.5	12 880
			SRPP	Placebo	6.5	12 669

MI, myocardial infarction; Max RPP, maximum rate pressure product; Max, maximal symptom limited exercise test; SRPP, same rate pressure product limited exercise test

Two separate procedures were used:

(1) Nine patients (group 1) underwent progressive maximal exercise testing to a symptomatic end-point followed by ^{201}Tl imaging on two separate occasions: (a) after intravenous administration of propranolol hydrochloride (0.2 mg/kg body weight), and (b) after intravenous administration of an equal volume of normal saline (placebo). Patients were randomly allocated to either propranolol-placebo or placebo-propranolol sequence.

(2) Six patients (group 2) were first studied after intravenous propranolol and then two weeks later after intravenous placebo. The placebo stress test was terminated when a rate pressure product similar to the maximum achieved during the propranolol scan had been attained. This part of the study was designed to assess if the effects of propranolol on the ^{201}Tl scans were entirely secondary to its effects on myocardial oxygen demand or if it had some other additional effect. Three patients in group 2 (cases 7, 8, 9) were also in group 1 and thus only required a third scan (to the same rate pressure product as on propranolol) to complete the second procedure. A total of 27 treadmill stress tests with subsequent ^{201}Tl myocardial imaging was therefore performed in the 12 patients.

TREADMILL STRESS TESTING

All patients were exercised on an Avionics E16 programmable treadmill using the standard Bruce procedure.⁴

Heart rate and electrocardiogram (leads CM4, CM5, CM6) were continuously monitored on an Avionics 3000 system. Systemic blood pressure was measured at regular intervals throughout the test using a sphygmomanometer.

The rate pressure product was calculated from heart rate and mean blood pressure (diastolic + one third pulse pressure). All exercise tests were performed by the same personnel using the same equipment at the same time of day and day of week for each subject. All subjects were in the postabsorptive state, had not smoked for at least 18 hours, and had stopped all drugs 48 hours before stress testing.

THALLIUM-201

Exercise and redistribution ^{201}Tl scans were performed using a sequential imaging technique. When each subject had reached his symptomatic exercise end-point, 1.5 to 2.0 mCi of thallous chloride was injected intravenously and exercise continued at the same work load for a further 60 seconds. The exercise images were obtained five minutes later using an Anger gamma camera (General Electric Maxi Camera II) fitted with a low energy, high resolution converging hole collimator (General Electric No. H2503 AD). A Varian series 71 computer system with 64K of memory interfaced to the gamma camera acquired images in 64×64 word mode. A 25% energy window was centred on the 69 to 83 KeV Hg-201 x-ray peak

and images containing 300 K counts were obtained in the anteroposterior, 45° left anterior oblique, and left lateral projections. Three to four hours later, patients were reimaged (redistribution scan) without further administration of ²⁰¹Tl using the same views.

A single nine point smooth followed by empirical background subtraction were used to process the images which were then displayed on a television screen using a 15 step colour scale. Two experienced observers, unaware both of the nature of the treadmill stress test and of the drug placebo sequence, interpreted the scans independently. In the few cases in which the observers disagreed, a consensus was reached.

IMAGE ANALYSIS

This was performed in three different ways.

Segment analysis

From the three views (anteroposterior, left anterior oblique, and left lateral) of each scan five different myocardial segments (anterior, anteroseptal, apex, inferior, and posterolateral—see Fig) were derived. A perfusion defect in any segment was defined as an area having a count density less than 75% of the maximum in that view, and such areas were recognised by superimposing a 75% contour line on the image. For segment analysis the presence or absence of a perfusion defect in any segment in any view was simply noted.

View analysis

In each view the percentage of the outer perimeter of left ventricular myocardium (excluding valve planes) represented by perfusion defects (count density <75% of maximum) was calculated by fitting a French curve to the left ventricular image and marking the defects on it. By straightening out the curve and measuring the length of the ventricular outer

perimeter and of the filling defects the percentage circumferential defect for each view was measured.

Patient analysis

The scintigraphic findings in each patient whether after propranolol or placebo were analysed to determine if the scan showed fixed or reversible perfusion defects suggestive of ischaemic heart disease.

The effect of propranolol administration on the ²⁰¹Tl images was determined (a) by comparing the corresponding five segments of the propranolol and placebo scans for presence or absence of perfusion defects, (b) by comparing the percentage circumferential defect in each of the corresponding views (anteroposterior, left anterior oblique, and left lateral) of the propranolol and placebo scans. A difference in size between corresponding defects equal to 25% or more of the larger defect was taken to be significant. Results are expressed (where appropriate) as mean ± SEM, and exercise time (min) and rate pressure product on propranolol and placebo compared by means of Student's paired t test.

Results

Good quality myocardial images were obtained in all subjects both after exercise and on redistribution. Their coronary artery lesions are shown in Table 2.

TREADMILL STRESS TESTING (Table 1)

Although seven of the nine patients in group 1 were able to exercise for a longer period after propranolol than after placebo, the mean exercise durations (propranolol 8.9 ± 2.4 vs placebo 7.9 ± 2.4 min) did not differ significantly ($p > 0.05$). Propranolol, however, caused a significant ($p < 0.05$) reduction in maximum rate pressure product ($11\,116 \pm 2349$ beats/min per mmHg) compared with placebo ($13\,964 \pm 3264$ beats/min per mmHg).

Fig Analysis of ²⁰¹Tl scans. For assessment of perfusion defects, the myocardial images were divided into five different segments—anterior (Ant), anteroseptal (AS), apex, inferior (Inf), and posterolateral (PL).

THALLIUM-201 SCINTIGRAPHY (Tables 2 to 4)

Group 1

(1) *Segmental analysis* (Tables 2, 4). In the nine patients, the 45 segments after propranolol were compared with the 45 corresponding segments after placebo in both the exercise and the redistribution scan, giving a total of 90 segment pairs for analysis. There was agreement as to presence or absence of perfusion defect in 54 out of the 90 segment pairs (60%). The remaining 36 segment pairs (40%) were discrepant: in 24 of 36 (67%) the placebo scan showed a perfusion defect, the propranolol scan being normal. In the remaining 12 discrepant segment pairs, the propranolol scan alone showed the abnormality.

(2) *View analysis* (Tables 3, 4). The three views after propranolol and after placebo were compared in the nine patients in both exercise and redistribution scans, giving a total of 54 view pairs for analysis. In 32 of them (59%) there was no significant difference in percentage circumferential defect between prop-

ranolol and placebo scans. In the remaining 22 (41%) view pairs, however, a significant difference in defect size was apparent, the larger defect occurring on the placebo scan in 19 (86%) view pairs and on the propranolol scan in only three (14%) instances. Six views containing a defect on the placebo scan were judged to be entirely normal on the propranolol scan whereas only one view was normal after placebo but abnormal after propranolol.

(3) *Patient analysis* (Table 4). After both propranolol and placebo seven of the nine patients displayed at least one perfusion defect allowing the correct diagnosis of ischaemic heart disease. One patient (case 8) had false negative scans after both propranolol and placebo. The last patient (case 9) had a normal scan in all views after propranolol (false negative scan), whereas the corresponding views after placebo showed anteroseptal and inferior perfusion defects correctly diagnosing ischaemic heart disease (this patient had lesions of left anterior descending and circumflex coronary arteries on angiography).

Table 2 Segmental analysis of thallium-201 scans after placebo (Plac) and propranolol (Prop)

Case No.		Abnormal segments on ²⁰¹ Tl scanning						Angiographic lesions
		Ant view		LAO view		Lat view		
		Plac	Prop	Plac	Prop	Plac	Prop	
Group 1								
1	Ex	I,AP	I	I,PL	I,AS	A,AP,I	A,AP	RCA,LAD,Cx
	R	I,AP	—	I,PL	—	A,AP	A	
2	Ex	I,AP	A,AP	I,AS	I,AS	A,AP	I,AP	LAD (RAC graft)
	R	—	A,AP	AS	AS	A	I,AP	
3	Ex	I	I,AP	—	—	I	I	RCA,Cx
	R	—	—	—	—	—	—	
4	Ex	—	—	I,PL	I,PL	A,AP	—	RCA
	R	—	—	I,PL	I,PL	A,AP	—	
5	Ex	I	I,AP	I,PL	PL	I	I	RCA,Cx
	R	I	I,AP	I,PL	PL	I	I	
6	Ex	I	I	I,PL	I	—	—	RCA,Cx,LAD
	R	I	—	—	—	—	—	
7	Ex	A	AP	—	—	A,AP	A	LAD
	R	A	AP	—	—	A,AP	A	
8	Ex	—	—	—	—	—	—	RCA,LAD
	R	—	—	—	—	—	—	
9	Ex	A,I	—	—	—	—	—	LAD,Cx
	R	—	—	—	—	—	—	
Group 2								
7	Ex	A	A,AP	—	I	A,AP	A,AP	LAD
	R	A	—	—	I	A,AP	A,AP	
8	Ex	—	—	—	—	—	—	RCA,LAD
	R	—	—	—	—	—	—	
9	Ex	AP	—	—	—	—	—	LAD,Cx
	R	AP	—	—	—	—	—	
10	Ex	—	—	I,AS	—	A,AP	A,AP	LAD
	R	—	—	—	—	AP	—	
11	Ex	—	—	I,PL	I,PL	I	—	LAD,Cx,RCA
	R	—	—	I,PL	PL	—	—	
12	Ex	AP,I	I	I	—	A,AP	A,AP	LAD,Cx
	R	—	—	PL	PL	—	A,AP	

A, anterior perfusion defect; AP, apical perfusion defect; I, inferior perfusion defect; PL, posterolateral perfusion defect; AS, anteroseptal perfusion defect; RCA, right coronary artery; LAD, left anterior descending coronary artery; Cx, circumflex coronary artery; Ex, exercise ²⁰¹Tl scan; R, redistribution ²⁰¹Tl scan.

Table 3 Percentage circumferential perfusion defects on thallium-201 scanning after placebo (Plac) and propranolol (Prop)

		Percentage circumferential defects on ²⁰¹ Tl scanning					
		Ant view		LAO view		Lat view	
		Plac	Prop	Plac	Prop	Plac	Prop
Group 1							
1	Ex	49*	31	59	48	39	30
	R	15*	0	43*	0	30*	14
2	Ex	3†	8	46*	30	63*	25
	R	0†	41	30*	13	48*	17
3	Ex	24*	5	0	0	19*	11
	R	0	0	0	0	0	0
4	Ex	0	0	52	59	25*	0
	R	0	0	45	58	20*	0
5	Ex	23	28	54	41	42	40
	R	23	22	48*	24	29	38
6	Ex	12*	9	56*	12	0	0
	R	16*	0	0	0	0	0
7	Ex	5†	35	0	0	51*	37
	R	4	4	0	0	50*	9
8	Ex	0	0	0	0	0	0
	R	0	0	0	0	0	0
9	Ex	45*	0	0	0	0	0
	R	0	0	0	0	0	0
Group 2							
7	Ex	5†	38	0†	5	51	50
	R	4*	0	0†	4	50*	25
8	Ex	0	0	0	0	0	0
	R	0	0	0	0	0	0
9	Ex	3*	0	0	0	0	0
	R	2*	0	0	0	0	0
10	Ex	0	0	31*	0	47*	20
	R	0	0	0	0	4*	0
11	Ex	0	0	48*	17	12*	0
	R	0	0	18	23	0	0
12	Ex	25	23	4*	0	55	64
	R	0	0	10	9	0†	29

*, View pair in which the placebo scan contained a significantly larger defect.

†, View pair in which the propranolol scan contained a significantly larger defect.

Ex, exercise ²⁰¹Tl scan; R, redistribution ²⁰¹Tl scan.Table 4 Comparison of ²⁰¹Tl scans after placebo and propranolol

Group	Type of analysis	Total No.	No. disagreeing	No. with positive placebo scan only	No. with positive propranolol scan only
1	Segmental	90	36	24	12
	View	54	22	19	3
	No. of cases	9	1	1	0
2	Segmental	60	16	10	6
	View	36	14	10	4
	No. of cases	6	0	0	0

Group 2

(1) **Segmental analysis** (Tables 2, 4). The six subjects in group 2 exercised after propranolol and again after placebo to the same rate pressure product as after propranolol. They were scanned after both exercise and redistribution, presenting 60 segment pairs for analysis. In 44/60 (73%) there was agreement between propranolol and placebo scans. Of the remaining 16 segment pairs, 10 (63%) were abnormal after placebo but normal after propranolol, and the remaining six segment pairs showed the converse (abnormal after propranolol but normal after placebo).

(2) **View analysis** (Tables 3, 4). The exercise and redistribution scans in the six patients provided 36 view pairs for analysis. In 22 of 36 (61%) view pairs there was agreement on percentage circumferential defect in propranolol and placebo scans. Significantly larger defects were, however, seen after placebo compared with propranolol in 10 of the 14 remaining view pairs (71%), the defects being larger after propranolol than after placebo in only four view pairs (29%). Seven views judged to be entirely normal after propranolol were abnormal on placebo, only two views being normal after placebo and abnormal after propranolol.

(3) *Patient analysis* (Table 4). One patient (case 8) had normal (false negative) scans after both propranolol and placebo. The other five patients all had a defect in at least one view after both interventions.

Discussion

Few studies concerning the effects of beta blocking drugs on the sensitivity and specificity of ^{201}Tl myocardial imaging have been reported. Pohost *et al.*⁵ in a series of 227 patients found no overall loss of sensitivity in patients taking propranolol (84%) compared with those not taking the drug (90%). In a subgroup of these patients with negative exercise electrocardiograms, however, propranolol was associated with a significant ($p < 0.05$) reduction in diagnostic sensitivity (76% v 90%). Albro *et al.*⁶ also found that the proportion of patients showing defects on ^{201}Tl scanning after dipyridamole stress was smaller in those on propranolol (63%) than in the others (82%), though this difference was not significant.

In the present study, propranolol administration considerably reduced both the number and extent of ^{201}Tl perfusion defects. In 24 of the 90 segment pairs recorded (27%) a defect occurred after placebo but not after propranolol and the majority of these defects were true positives (Table 2) since only four (17%) occurred in areas of myocardium supplied by angiographically undiseased coronary arteries. Matched perfusion defects were also significantly smaller after propranolol compared with placebo in 19 of 54 (35%) of cases. These changes resulted in one subject having an entirely normal ^{201}Tl study on propranolol despite the presence of anterior and inferior defects on the placebo scan and angiographic left anterior descending and circumflex coronary artery disease. Scintigraphy on propranolol in this patient would have been falsely negative and the diagnosis of ischaemic heart disease missed altogether. Much less commonly the opposite changes occurred with unmatched defects being restricted to the propranolol scan or matched defects being significantly larger after its use.

Two possible mechanisms may underlie these effects. Firstly, they may result from drug induced changes in patients' exercise performance. The acute administration of propranolol⁷ blunts the normal rise in heart rate and systolic blood pressure occurring at each stage of upright exercise, resulting in a pronounced reduction in the rate pressure product which tends to reflect similar changes in myocardial oxygen consumption⁸ even in the presence of propranolol treatment.⁹ In addition to these effects, propranolol may also increase myocardial oxygen extraction and augment stroke volume despite a tendency for the cardiac output to fall. The overall effect of these changes on exercise ability depends on the underlying

left ventricular function. Normal subjects tend to perform less well after the drug, whereas patients with coronary artery disease and impaired left ventricular function show the greatest and most consistent increase in exercise performance.⁷ The end result in terms of the effect of propranolol on exercise ^{201}Tl scintigraphy is that these beneficial changes may postpone the point at which myocardial ischaemia appears beyond that at which exhaustion limits the exercise test. Thus, exercise may be terminated before diagnostic perfusion defects can be induced.

In order to investigate whether changes in exercise performance and myocardial oxygen demand were responsible for the reduced diagnostic sensitivity of scanning while on propranolol, six patients (group 2) were exercised to the same rate pressure product on placebo and propranolol. Despite the fact that corresponding scans were thus obtained after exercise requiring similar degrees of myocardial oxygen consumption, 17% (10/60) of segment pairs again showed a perfusion defect on the placebo scan alone and such defects were again significantly smaller in 28% (10/36) of view pairs after propranolol. The loss of sensitivity associated with scanning in the presence of propranolol thus seemed unrelated to the myocardial oxygen demand and hence to the principal effect of the drug on exercise performance.

The second possible underlying mechanism is a propranolol induced change in ^{201}Tl myocardial extraction. Propranolol has been shown in resting animals without coronary artery disease to reduce Tl uptake by 11 to 32%^{1,2} possibly as a result of the reduction in coronary flow which often accompanies beta blockade.¹⁰ Similar reductions in coronary flow and thallium extraction after beta blockade in man might vary substantially in degree from region to region, since flow in non-ischaemic regions that are readily accessible to the drug may be reduced to a greater extent than that in regions supplied by stenosed coronary arteries which both impede the delivery of propranolol and, as a result of atheromatous disease, tend to be less reactive to vaso-active stimuli. In this way, regional differences in ^{201}Tl distribution which would normally result in a recognisable perfusion defect may be lessened or even obscured by treatment with propranolol.¹¹

We believe this study has shown that ^{201}Tl scanning in the presence of propranolol is subject to loss of sensitivity which may be manifested as a reduction in the true incidence and size of perfusion defects. As a result, the extent of disease (number of vessels involved) may be underestimated or, as in one patient in this study, the diagnosis of coronary artery disease be missed altogether. In view of these findings, it seems prudent to withdraw propranolol before performing exercise ^{201}Tl imaging, bearing in mind poss-

ible deleterious effects of sudden withdrawal.^{12 13} Alternatively, negative tests may be repeated when the patient has been weaned off propranolol. In any case, it is clear that in patients taking propranolol, negative results do not exclude coronary artery disease whereas the presence of perfusion defects does accurately reflect the presence of disease though not its true extent.

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Requests for reprints to Dr M M Webb-Peploe, Department of Cardiology, St Thomas's Hospital, London SE1 7EH.