INTRINSIC HEART RATE ON EXERCISE AND THE MEASUREMENT OF β -ADRENOCEPTOR BLOCKADE

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1 Methods of expressing the effects of β -adrenoceptor blocking drugs on exercise heart rate have been evaluated using a standardised exercise test.

2 In six normal subjects given atropine (0.04 mg/kg) on two separate occasions, the mean $\pm$ s.e. mean exercise heart rate rose by 10.3 ± 1.8 beats/min and by 11.0 ± 1.6 beats/min respectively. This increase was designated the 'vagal effect' and was not significantly different in the two studies.

3 After atropinisation, propranolol (0.2 mg/kg) reduced mean $\pm$ s.e. mean exercise heart rate by 45.3 ± 2.6 beats/min and 0.4 mg/kg by 50.8 ± 4.5 beats/min. This mean sympathetic blockade was not altered significantly by increasing the dose of propranolol but, in four of the six subjects, the larger dose produced an increased effect of 4, 6, 12 and 16 beats/min, suggesting that maximum sympathetic blockade may not have been produced by 0.2 mg/kg.

4 Knowledge of the vagal effect in each subject with standardised exercise enabled prediction to be made of the exercise heart rate after propranolol (0.4 mg/kg) without previous atropinisation. Propranolol (0.4 mg/kg) was then given intravenously to each subject and the actual exercise heart rate measured. There was no significant difference between the predicted and observed exercise heart rates.

5 Propranolol (0.6 mg/kg) without atropine was then given to the four subjects who had shown increased effect with (0.4 mg/kg) and the sympathetic blockade was measured. In one subject, a further increase in sympathetic blockade of 10 beats/min was found.

6 The intrinsic heart rate at rest and on exercise was measured for propranolol (0.2 and 0.4 mg/kg) and, for propranolol (0.6 mg/kg), the intrinsic heart rate on exercise was calculated. At rest, although no significant difference was found between the two dose levels, three subjects did not appear to have maximum autonomic blockade at 0.2 mg/kg. Similarly, several subjects had lower intrinsic heart rates on exercise after 0.4 or 0.6 mg/kg than after 0.2 mg/kg. The intrinsic heart rate on exercise was significantly greater than that obtained at rest.

7 Using the maximum sympathetic blockade obtained in each subject as the sympathetic component of exercise, the effects of increasing oral doses of practolol on exercise heart were measured as percentage blockade of sympathetic effect and this was compared with other conventional methods of measuring β -adrenoceptor blockade. It was found that percentage blockade of sympathetic effect correlated most closely with both percentage and absolute reduction of exercise heart rate. Correlations with exercise heart rate after drug and percentage inhibition of tachycardia, whilst also significant, did not appear as good.

8 When the effects of practolol were expressed in terms of the potential blockade, a plateau occurred between 70 and 80% of 'maximum' sympathetic blockade. The failure to achieve higher levels with practolol may be the result of its partial agonist or intrinsic sympathomimetic activity.

Introduction

The reduction in exercise heart rate produced by β -adrenoceptor blocking drugs has been used as a measure of their efficacy (Brick, Hutchison, McDevitt, Roddie & Shanks, 1968; Fitzgerald &

Scales, 1968; Kofi Ekue, Lowe & Shanks, 1970; Coltart & Shand, 1970; Bodem & Chidsey, 1973). There has, however, been a lack of agreement about how the effects of a drug on heart rate

should be presented. Thus measurements of β -adrenoceptor blockade include comparison of the absolute heart rate before and after drug administration (Brick *et al.*, 1968; Kofi Ekue *et al.*, 1970), the percentage inhibition of exercise tachycardia (Fitzgerald & Scales, 1968), the percentage blockade of sympathetic activity (Coltart & Shand, 1970), the reduction of control exercise heart rate (Bodem & Chidsey, 1973) and the percentage reduction of exercise heart rate (Carruthers, Kelly, McDevitt & Shanks, 1974).

The absolute exercise heart rate (EHR) after drug administration and the reduction (R) from the control exercise heart rate are self-explanatory. The percentage reduction (%R) is derived by expressing the absolute reduction (R) as a percentage of the control exercise heart rate. Fitzgerald & Scales (1970) measured the change in heart rate from rest to exercise and used the term 'percentage inhibition of exercise tachycardia' (%I) to describe the reduction produced by β -adrenoceptor blockade. The method of Coltart & Shand (1970) was to call the reduction in exercise heart rate 15 min after the administration of propranolol (0.3 mg/kg intravenously) 'maximum', based on flattening of oral dose-response curves after propranolol (40-120 mg) and the assumption that no vagal inhibition persisted at the exercise heart rates attained. The reductions in heart rate produced by smaller doses of propranolol were then expressed as a percentage of this effect, i.e., 'percentage blockade of maximum sympathetic activity'.

The present study was undertaken to evaluate these methods of expressing the effects of β -adrenoceptor blocking drugs on exercise heart rate. This necessitated the investigation of the 'intrinsic heart rate' (Jose, 1966) on exercise so that true sympathetic activity could be calculated both in control studies and after β -adrenoceptor blocking drugs had been given. The effects of the drugs could then be expressed as percentage blockade of sympathetic activity (%B) and this figure was then compared with the other methods of expression outlined above. In addition, the reproducibility of the vagal component of autonomic activity during standardised exercise was investigated.

Methods

Subjects were healthy males aged 24-38 years. All were familiar with the expected effects of the drugs to be used and volunteered for the study after full explanation.

Exercise was performed by stepping on and off a box 46 cm high at a rate of 32 steps/min for

3 min. Heart rate was recorded on standard Lead I of a direct writing electro cardiograph within 5 s of completing exercise, and was calculated from the time taken for 5 complete cardiac cycles.

Six subjects performed the exercise test before and after autonomic blockade with atropine and propranolol. After a period of control exercise, each subject rested for 10 min before receiving atropine (0.04 mg/kg) intravenously over 3 min. Exercise was repeated and each subject rested for a further period of 10 min before receiving propranolol (0.2 mg/kg) intravenously over 3 min. Each subject then performed a third and final period of exercise. The entire study was repeated on a separate occasion at least 7 days later, using propranolol (0.4 mg/kg) intravenously instead of 0.2 mg/kg.

Each of these subjects was given propranolol (0.4 mg/kg) intravenously on a second occasion without previous atropinisation and exercise heart rate was measured both before and after drug; and four of the six subjects, who showed a greater reduction in exercise heart rate after propranolol (0.4 mg/kg) than they had after 0.2 mg/kg, were given propranolol (0.6 mg/kg) intravenously over 3 min and exercise heart rate recorded. Again no atropine was given.

From studies previously published (Carruthers *et al.*, 1974) on resting and exercise heart rates before and at 2 and 24 h after multiple oral doses of practolol ranging from 25 to 800 mg in the same six subjects, it was possible to calculate the absolute exercise heart rate (EHR), the reduction (R) from control exercise heart rate, the percentage reduction (%R) of exercise heart rate and the percentage inhibition (%I) of exercise tachycardia. The percentage blockade (%B) of sympathetic activity was calculated from the reduction (R) expressed as a percentage of the maximum blockade produced by intravenous propranolol. Comparison was made between the percentage blockade (%B) and the various other parameters.

Statistical analysis were carried out using Students' *t*-test; correlation and regression coefficients were calculated by the method of least squares.

Results

The effects of intravenous atropine and propranolol on exercise heart rate are shown in Table 1. Control exercise heart rates ranged from 125-180 beats/min with a mean $\pm$ s.e. mean of 154.0 ± 7.1 beats/min on the first occasion and of 155.3 ± 6.8 beats/min on the second. These were not statistically different, and the maximum difference seen within subjects was 8 beats/min.

After atropine (0.04 mg/kg), the mean $\pm$ s.e. mean exercise heart rate rose significantly on both occasions, by 10.3 ± 1.8 and by 11.0 ± 1.6 beats/min respectively. This increase was designated the 'vagal effect' and was not significantly different in the two studies. Of the six subjects, three showed the same increase on both occasions, two showed a variation of only 1 beat/min and one varied by 2 beats/min. There was a significant inverse correlation between control exercise heart rate and vagal activity ($r = -0.89$; $P < 0.001$).

When propranolol (0.2 mg/kg) was given, mean $\pm$ s.e. mean exercise heart rate fell significantly to 119.0 ± 4.3 beats/min. This gave a mean $\pm$ s.e. mean sympathetic component of 45.3 ± 2.6 beats/min to the exercise heart rate (Table 1). After propranolol (0.4 mg/kg), the exercise heart rate was 115.5 beats/min, a mean $\pm$ s.e. mean decrease of 50.8 ± 4.5 beats/min. Thus propranolol (0.4 mg/kg) did not produce a significantly greater effect than the smaller dose. However, in terms of individual response, the

larger propranolol dose produced increases in the measured sympathetic blockade of 4, 6, 12 and 16 beats/min in four of the six subjects (Table 1). With propranolol (0.4 mg/kg) there was a direct correlation between control exercise heart rate and the sympathetic component ($r = 0.84$; $P < 0.05$). In addition, with this dose (but not with 0.2 mg/kg), there was an inverse correlation between the vagal and sympathetic components of exercise heart rate ($r = -0.89$; $P < 0.01$).

The similarities between the vagal activity during standardised exercise measured in the same subjects after atropine on two separate occasions suggested that it might be possible to predict the vagal component of exercise during further exercise periods. This would enable further doses of propranolol to be evaluated without the inconvenience of administering atropine. To do this, the expected exercise heart rate in each subject after propranolol (0.4 mg/kg) intravenously without atropine was calculated by subtracting the mean vagal activity ('vagal effect' in Table 1) on the two

Table 1 The influence on exercise heart rate (beats/min) of vagal and sympathetic activity

I Atropine (0.04 mg/kg i.v.) followed by propranolol (0.2 mg/kg i.v.)					
Subject	Control (a)	Post- atropine (b)	Post- propranolol (c)	Vagal effect (b-a)	Sympathetic component (b-c)
A	155	162	112	7	50
B	180	185	132	5	53
C	153	165	128	12	37
D	154	167	118	13	49
E	157	165	121	8	44
F	125	142	103	17	39
Mean	154.0	164.3	119.0	10.3	45.3
s.e. mean	7.1	5.6	4.3	1.8	2.6

II Atropine (0.04 mg/kg i.v.) followed by propranolol (0.4 mg/kg i.v.)					
Subject	Control (a)	Post- atropine (b)	Post- propranolol (c)	Vagal effect (b-a)	Sympathetic component (b-c)
A	156	164	108	8	56
B	177	183	118	6	65
C	155	167	126	12	41
D	152	165	121	13	44
E	165	175	115	10	60
F	127	144	105	17	39
Mean	155.3	166.3	115.5	11.0	50.8
s.e. mean	6.8	5.4	3.2	1.6	4.5

No significant differences exist between similar columns in I and II.

occasions from the post-propranolol heart rate in Table 1 II(c). Propranolol (0.4 mg/kg) intravenously was then given to each subject over 3 min and the standardised exercise test performed. The exercise rates observed in each subject are shown in Table 2, together with the predicted or calculated rates. There was no significant difference between the observed and calculated exercise heart rates. In three subjects, they were identical; in the other three, variations of up to 4 beats/min were seen.

Because the vagal activity is constant for standardised exercise and predictions such as described above are valid, the sympathetic activity can be measured by the difference between the control exercise heart rate and that obtained after propranolol alone, as well as by the difference between the post-atropine and post-atropine plus propranolol exercise heart rates (shown in Table 1). The former method was used to assess the effects of propranolol (0.6 mg/kg) intravenously in four subjects. The results are shown in Table 3, expressed as the sympathetic component, and compared with the results obtained in the previously outlined studies. In one subject (B) a

further increase in sympathetic blockade of 10 beats/min was found, but in the other three no substantial change was obtained. The overall differences seen with increasing doses were not significant, but it can be seen from Table 3 that two subjects appeared to get maximum sympathetic blockade on exercise with propranolol (0.2 mg/kg), two others required 0.4 mg/kg and in one or perhaps two subjects, maximum blockade was only produced by 0.6 mg/kg. The maximum sympathetic component of exercise in each individual was, therefore, calculated. In subject B, the maximum may not have been reached but it was felt that larger doses of propranolol should not be given.

Table 4 shows the intrinsic heart rates measured in the six subjects both at rest and on exercise after atropine (0.04 mg/kg) and propranolol (0.2 and 0.4 mg/kg) had been given intravenously. In addition, the intrinsic heart rate on exercise after propranolol (0.6 mg/kg) has been calculated by adding the vagal activity to the post-propranolol exercise heart rate. The differences between the effects of propranolol (0.2 and 0.4 mg/kg) both at rest and on exercise are not significant. However,

Table 2 Actual exercise heart rate (EHR beats/min) obtained after propranolol (0.4 mg/kg i.v.) compared with predicted exercise heart rate, calculated after atropine (0.04 mg/kg i.v.) and propranolol (0.4 mg/kg i.v.)

		Subject					
		A	B	C	D	E	F
EHR after propranolol (0.4 mg/kg i.v.)	Observed	104	112	118	108	106	90
	Calculated **	100	112	114	108	106	88

** Calculated = Post-propranolol rate (Table 1 II)—Mean vagal effect (Table 1 I and II).

Observed v Calculated $t = 2.0761$; $0.1 > P > 0.05$

Table 3 Sympathetic component of exercise heart rate (beats/min) after atropine and propranolol (0.2 and 0.4 mg/kg i.v.) compared with estimated component after propranolol alone (0.4 and 0.6 mg/kg i.v.) in six subjects

Subject	After propranolol and atropine		After propranolol alone		Maximum effect	
	(0.2 mg/kg)	(0.4 mg/kg)	(0.4 mg/kg)	(0.6 mg/kg)	Propranolol (mg/kg)	Sympathetic component
A	50	56	52	54	0.4	56
B	53	65	65	75	0.6	75
C	37	41	37	41	0.4	41
D	49	44	44	—	0.2	49
E	44	60	59	62	0.6	62
F	39	39	37	—	0.2	39

0.2 mg/kg v 0.4 mg/kg $t = -1.7524$; $0.2 > P > 0.1$

0.4 mg/kg (+ atropine) v 0.4 mg/kg (calc) $t = 2.4474$; $0.1 > P > 0.05$

0.4 mg/kg v 0.6 mg/kg $t = -2.6433$; $0.1 > P > 0.05$

at rest the maximum does not appear to have been achieved after 0.2 mg/kg in three subjects, and similarly on exercise several subjects had lower heart rates after 0.4 or 0.6 mg/kg than after 0.2 mg/kg. At both propranolol dose levels and also with minimum heart rates achieved in each subject, the intrinsic heart rate on exercise was significantly higher than that obtained at rest.

Finally, the maximum sympathetic activity engendered in each subject on exercise was used to re-analyse results of a practolol dose-response curve reported by Curruthers *et al.*, (1974) in the same six subjects using the same exercise test. From the sympathetic component, the percentage of true β -adrenergic receptor blockade (%B) was determined and this was compared with other standard methods of assessing β -adrenoceptor blockade after exercise. The detailed results are shown in Table 5 and the correlations obtained between %B and the other parameters are shown in Table 6. It can be seen that significant correlations were obtained in each case, ranging from 0.48-0.81. The best correlations appeared to be with percentage reduction of exercise heart rate and reduction from control exercise heart rate.

Discussion

Chamberlain, Turner & Sneddon (1967) showed that maximum inhibition of vagal control of the sinoatrial node in normal volunteers could be achieved both at rest and during exercise by intravenous atropine (0.04 mg/kg). Using this dose

of atropine in combination with intravenous propranolol (0.2 mg/kg) in man, Jose (1966) claimed that the heart was totally blocked to the chronotropic response to vagal or sympathetic stimuli and to the inotropic response to isoprenaline for 20 min. The resultant measurement he called 'the intrinsic heart rate', indicating that the heart was liberated from the influences of the autonomic nervous system.

The heart rate is controlled by the autonomic nervous system not only at rest but also on exercise (Robinson, Epstein, Beiser & Braunwald, 1966); generally the lower the level of exercise, the greater the element of vagal activity. At the higher levels of exercise, control is predominantly sympathetic but exercise heart rates of the order of 200 beats/min are required before vagal tone is completely absent (Robinson, Percy, Brueckman, Nicholas & Miller, 1953). Thus with a standardised exercise test, it should be possible to evaluate the separate roles of the parasympathetic and sympathetic nervous systems by the use of atropine and propranolol and to produce a level of heart rate on exercise devoid of autonomic control which may be termed 'the intrinsic heart rate on exercise'.

The increase in mean exercise heart rate of 10 or 11 beats/min produced by vagal blockade with atropine is similar to that demonstrated by other workers at similar exercise heart rates (Robinson *et al.*, 1953; Robinson *et al.*, 1966; Chamberlain *et al.*, 1967). The results of the present study show that atropine (0.04 mg/kg) given intravenously unfolds a component of vagal activity which is

Table 4 Intrinsic rate (IHR beats/min) at rest and after exercise with atropine (0.04 mg/kg i.v.) and propranolol (0.2 and 0.4 mg/kg i.v.) and calculated after propranolol (0.6 mg/kg i.v.)

Subject	Intrinsic heart rate (beats/min)				
	Rest		Propranolol (mg/kg)		
	0.2	0.4	Exercise		
			0.2	0.4	0.6 (Calculated)
A	89	88	112	108	111
B	109	98	132	118	108
C	112	105	128	126	124
D	96	99	118	121	—
E	99	94	121	115	113
F	86	90	103	105	—
Mean	98.5	95.7	119.0	115.5	114.0
s.e. mean	4.3	2.6	4.3	3.2	3.5

IHR rest 0.2 v 0.4 : $t = 1.1804$: $P > 0.2$

IHR exercise 0.2 v 0.4 : $t = 1.3853$: $P > 0.2$

IHR rest 0.2 v exercise 0.2 : $t = -15.9592$: $P < 0.001$

IHR rest 0.4 v exercise 0.4 : $t = -19.5634$: $P < 0.001$

Minimum IHR rest v minimum IHR exercise : $t = -10.4821$: $P < 0.001$

Table 5 Effects of practolol (25-800 mg orally) 2 h and 24 h after administration on exercise heart rate in six subjects—comparison of different methods of assessment

(a) 2 h													
Subject	EHR	Practolol (25 mg)			Practolol (50 mg)			Practolol (100 mg)			Practolol (100 mg)		
		R	%R	%I	EHR	R	%R	%I	EHR	R	%R	%I	%B
A	124	32	20.5	-0.3	122	36	22.8	10.5	117	37	24.0	17.4	66.1
B	136	22	13.9	21.3	128	36	22.0	34.7	126	37	22.7	43.7	49.3
C	120	27	18.4	5.9	128	28	17.9	22.1	120	40	25.0	31.7	97.6
D	143	17	10.6	9.4	124	32	20.5	27.6	108	46	29.9	31.9	93.8
E	136	19	12.3	18.0	120	28	18.9	20.0	125	25	16.7	21.0	40.3
F	104	22	17.5	33.3	100	24	19.4	45.2	96	24	20.0	-3.4	61.5
Mean	127	23.2	15.5	14.4	120	30.7	20.3	26.7	115	34.8	23.1	23.7	68.1
s.e. mean	6	2.2	1.6	5.1	4	2.0	0.8	5.0	5	3.5	1.8	6.7	9.5
(b) 24 h													
Subject	Sympathetic activity (beats/min) based on maximum blockade with propranolol i.v.				EHR	Practolol (50 mg)			Practolol (100 mg)				
						R	%R	%I	EHR	R	%R	%I	%B
A	56				146	12	7.6	2.3	132	22	14.3	3.5	39.3
B	75				147	17	10.4	5.6	136	27	16.6	37.9	36.0
C	41				138	18	11.5	7.4	132	28	17.5	26.8	68.3
D	49				136	20	12.8	7.9	142	12	7.8	5.8	24.5
E	62				136	12	8.1	11.7	126	24	16.0	12.9	38.7
F	39				113	11	8.9	2.4	100	20	16.7	11.1	51.3
Mean	53.7				136	15.0	9.9	6.3	128	22.2	14.8	16.3	43.0
s.e. mean	5.6				5	1.6	0.8	1.5	6	2.4	1.5	5.5	6.1

(a) 2 h

Subject	EHR	Practolol (200 mg)			EHR	Practolol (400 mg)			EHR	Practolol (800 mg)		
		R	%R	%I		R	%R	%I		R	%R	%I
A	114	43	27.4	24.4	116	40	25.6	16.1	114	46	28.8	23.6
B	129	36	26.3	23.2	128	37	22.4	28.6	122	48	28.2	41.7
C	120	50	29.4	49.5	128	28	18.0	41.1	122	33	21.3	40.0
D	122	38	23.8	31.9	126	46	26.7	42.9	112	40	26.3	41.3
E	119	35	22.7	35.3	104	56	35.0	48.7	113	50	30.7	47.4
F	98	25	20.3	39.0	100	30	23.1	36.1	98	27	21.6	37.1
Mean	117	39.5	25.0	33.9	117	39.5	25.1	25.6	114	40.7	26.2	38.5
s.e. mean	4	3.6	1.4	4.0	5	4.2	2.3	4.8	4	3.7	1.6	3.3

(b) 24 h

Subject	EHR	Practolol (200 mg)			EHR	Practolol (400 mg)			EHR	Practolol (800 mg)		
		R	%R	%I		R	%R	%I		R	%R	%I
A	134	23	14.6	11.1	122	34	21.8	18.5	128	32	20.0	13.9
B	135	40	22.9	21.7	128	37	22.4	14.3	116	54	31.8	36.1
C	130	40	23.5	53.6	128	28	18.0	26.7	128	27	17.4	31.4
D	124	36	22.5	41.8	128	44	25.6	25.5	118	34	22.4	38.7
E	127	27	17.5	29.0	115	45	28.1	52.6	116	47	28.8	56.4
F	102	21	17.1	19.5	98	32	24.6	36.1	106	19	15.2	25.7
Mean	125	31.2	19.7	29.5	120	26.7	23.4	29.0	119	35.5	22.6	33.7
s.e. mean	5	3.5	1.5	6.4	5	2.8	1.4	5.6	3	5.3	2.6	5.8

EHR Exercise heart rate after drug administration (beats/min);

R Reduction in control exercise heart rate (beats/min);

%R Percentage reduction of control exercise heart rate;

%I Percentage inhibition of exercise tachycardia;

%B Percentage blockade of sympathetic activity.

reproducible in the same subject for standardised exercise. This suggests that, under controlled conditions, the vagal activity can be measured one or two times initially but subsequently can be predicted, thus preventing repeated exposure to the unpleasant side effects of atropinisation.

Even at rest, propranolol (0.2 mg/kg) intravenously did not appear to produce maximum β -adrenoceptor blockade in all subjects. In three out of six subjects further reductions in heart rate were obtained after propranolol (0.4 mg/kg) was given, even though the overall effect of the increased dosage in the group was not significant. Similarly, after exercise, maximum reductions in exercise heart rate were seen after 0.2 mg/kg in only two subjects. The others required 0.4 mg/kg (two subjects) or 0.6 mg/kg (two subjects) for maximum effect and even then, it was not certain that one of the subjects had reached his maximum. However as this subject's exercise heart rate after 0.6 mg/kg was similar to the maximum reduction achieved by the others, it was decided not to increase the dose further. The measurement of intrinsic heart rate both at rest and on exercise would, therefore, appear to require selection of propranolol dose in each subject unless unnecessarily large doses are to be given to some. Intrinsic heart rate at rest in this present study was assessed with the subjects standing upright and this probably accounts for the differences in propranolol dosage required when compared to Jose (1966) whose subjects were lying supine. The observation that subjects with the highest exercise heart rates had the greatest contribution of sympathetic activity and the least vagal activity agrees with the findings of Chamberlain *et al.*, (1967).

The intrinsic heart rates at rest ranged from 86 to 105 beats/min and on exercise from 103 to 124 beats/min. Subjects with the highest rates at rest also had the highest rates on exercise. In all cases the intrinsic heart rate on exercise was higher than that recorded at rest and the differences between the two were significant. The range of the differences was from 10-20 beats/min. Assuming that

autonomic blockade had occurred both at rest and on exercise, it is necessary to explain why the heart rate increases with exercise. In patients after cardiac transplantation, the heart rate increases with exercise due to the effects of circulating endogenous catecholamines acting on intact receptors in the myocardium (Kent & Cooper, 1974) and it has been shown in greyhounds that this increase can be prevented by β -adrenoceptor blockade (Donald, 1974). However, a small rise in heart rate during exercise persists after bilateral adrenalectomy and the mechanism for the catecholamine-independent increase is not clear. Presumably, this mechanism may have been operating in our normal subjects after autonomic blockade as the alternative explanation would appear to be that blockade was incomplete and this seems unlikely in the practical sense, even though recognising that with competitive blockade 100% effect cannot be obtained.

Identification of the vagal component of exercise heart rate and measurement of intrinsic heart rate on exercise enabled the sympathetic component of exercise to be quantitated. This varied from 39-75 beats/min (mean $\pm$ s.e. mean 53.7 ± 5.6) in the six subjects. The effects of practolol could then be expressed as percentage blockade of total sympathetic activity and comparison was made with other conventional methods of assessing β -adrenoceptor blockade.

Because of the considerable inter-subject variation in control exercise heart rate it is hardly surprising that the correlation of rate after drug with percentage blockade was rather poor ($r = 0.48$). Variation in resting heart rate, possibly related to emotional status, and the variable response of resting heart rate to β -adrenoceptor blockade, are inherent shortcomings in the assessment of effect by percentage inhibition of tachycardia (Kofi Ekue *et al.*, 1970). However, the correlation with percentage blockade indicates that there is some value in the technique ($r = 0.62$; $P < 0.001$). The absolute reduction ($r = 0.78$) and the percentage reduction of exercise heart rate

Table 6 Correlation coefficients between percentage blockade of sympathetic activity and other parameters of β -adrenoceptor blockade

	Correlation coefficient (<i>r</i>)
% B ν Absolute exercise heart rate (EHR)	-0.48*
% B ν Reduction from control exercise rate (R)	0.78*
% B ν Percentage reduction of exercise heart rate (% R)	0.81*
% B ν Percentage inhibition of exercise tachycardia (% I)	0.62*

* $P < 0.001$

($r = 0.91$) demonstrated the best relationships with the specific measurement of sympathetic blockade. The calculation of reduction and percentage reduction of exercise heart rate depend only on knowledge of the control exercise heart rate and the exercise heart rate after the administration of β -adrenoceptor blocking drugs and may be measured without prior knowledge of total sympathetic activity in each of the subjects studied. These simple measurements are clearly the most suitable of the available methods of expressing β -adrenoceptor blockade at this level of exertion.

It must be pointed out that periods of up to 2 years elapsed between the original studies by Carruthers *et al.*, (1974) on the effects of increasing doses of practolol on exercise heart rate and the observations reported in this study. It is known that intrinsic heart rate is proportional to

age (Jose, 1966) and, therefore, presumably alterations in sympathetic activity may also occur. Nevertheless, the original regression lines of Jose & Collison (1970) suggest that little change occurs in normal subjects over such a short period. Thus these results are unlikely to be invalidated by this fact.

In conclusion, an observation can be made on the β -adrenoceptor blocking ability of practolol. When the effects of practolol were expressed in terms of the potential blockade, a plateau response occurred with practolol between 70 and 80 per cent of 'maximum' sympathetic blockade. The failure to achieve higher levels with practolol would appear to be the result of its partial agonist or intrinsic sympathomimetic activity.

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