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FAILURE OF PROPRANOLOL AND METOPROLOL TO ALTER VENTILATORY RESPONSES TO CARBON DIOXIDE AND EXERCISE

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1 Neither propranolol (80 mg) nor metoprolol (100 mg) given orally to eight normal subjects altered mean ventilatory responses to carbon dioxide or to moderate graded exercise.

2 Incremental doses of the drugs to totals of 320 mg propranolol and 400 mg metoprolol also did not affect these ventilatory responses.

3 Both drugs markedly decreased the heart rate response to exercise.

4 Neither propranolol nor metoprolol are likely to cause CO_2 retention by an effect on the ventilatory responses to inhaled carbon dioxide or to exercise.

Introduction

Reduced hyperoxic ventilatory responses to carbon dioxide have recently been described in normal subjects following oral doses of 80 mg propranolol, a β-sympathetic receptor blocking agent (Mustchin, Gubbin, Tattersfield & George, 1976). This finding is consistent with our own earlier observations of increased hyperoxic ventilatory responses to carbon dioxide during intravenous infusion of salbutamol, a β-sympathominetic agent (Leitch, Clancy, Costello & Flenley, 1976). Both these observations suggest that catecholamines may have a central effect on ventilation but are inconsistent with much animal and human experimental evidence indicating that catecholamines influence ventilation only by mechanisms mediated through the carotid bodies and that these effects are blocked by hyperoxia (Cunningham, Lloyd & Patrick, 1963; Cunningham, Hey, Patrick & Lloyd, 1963; Joels & White, 1968; Heistad, Wheeler, Mark, Schmid & Abboud, 1972). If catecholamines only influence ventilation by carotid body mediated mechanisms, then β-adrenoceptor blocking drugs should not influence the hyperoxic ventilatory response to carbon dioxide, for adrenergic effects on carotid body activity are abolished by hyperoxia. We have, therefore, sought changes in the hyperoxic ventilatory response to carbon dioxide after administration of the β-adrenoceptor blocking agents, propranolol and metoprolol. Because Mustchin *et al.* (1976) stated, without data, that ventilatory responses to exercise were diminished by propranolol, an effect which could be of clinical significance, we have extended our studies to include responses to standardized progressive exercise tests.

Methods

Eight healthy non-asthmatic male subjects aged 22–32 years, weighing 66–79 kg gave informed consent to the measurement of their ventilatory responses to CO_2 and exercise following administration of placebo, propranolol 80 mg or metoprolol 100 mg orally. Four of the subjects, all medically qualified, consented to further studies with higher doses of the drugs. All studies were approved by the South Lothian District Advisory Ethical Committee.

Ventilatory response to carbon dioxide in hyperoxia was measured using a rebreathing method (Read, 1967) with a bag-in-box technique. The rebreathing bag initially contained 7% CO_2/93% O_2. P_{CO_2} in the bag was recorded using a Uras 4 CO_2 analyser which continuously sampled gas from and returned gas to the bag. Ventilation was recorded using a 120 litre Tissot spirometer modified to provide analogue and digital electrical signals proportional to volume. Ventilation and P_{CO_2} were recorded in analogue form with a Mingograf 81 (Elema, Stockholm) recorder and also digitally with a PDP 11 computer. From these records, mean values for ventilation and P_{CO_2} for each half-minute after the first half minute of rebreathing could be calculated and used to derive the regression of ventilation on P_{CO_2} by the method of least squares. This relation is linear and can be described by the equation $\dot{V}_E = S(P_{CO_2} - B)$ (Cunningham, Shaw, Lahiri & Lloyd, 1961), where B is the intercept on the horizontal P_{CO_2} axis obtained by extrapolating the $\dot{V}_E/P_{CO_2}$ line and S_{CO_2} is the slope of the line. This relationship could be plotted by the computer on an

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X—Y recorder, thus establishing a permanent record of the parameters (Clarkson, Leitch & McHardy, 1979). Mean values for S_{CO_2} and B_{CO_2} were derived from three studies on each occasion in each subject in order to minimise differences due to the known variability of CO_2 response measurements by the Read technique (Lyall, Bourne & Cameron, 1975). The coefficient of variation for repeated measurements of the ventilatory response to carbon dioxide in our laboratory is 18% (Clarkson *et al.*, 1979) and this compares favourably with Read's (1967) observations.

Progressive exercise testing was performed on an electrically braked bicycle ergometer (Elema). The initial work load was 17W (100 kpm/min) for the first 2 min increasing thereafter by steps of 17W (100 kpm/min) each minute until the sutject was unable to continue. The limiting factor for all subjects was found to be painful or tired legs. The electrocardiogram (lead CH4) was recorded and expired gas was collected in the Tissot spirometer during the last half minute of each work load, the expired gas being analysed for oxygen using a paramagnetic oxygen analyser (Servomex 101A) and carbon dioxide using an infra-red analyser (Uras 4). Values for ventilation and heart rate at standard oxygen uptakes of 44.6 mmol(1 litre STPD/min) and 66.9 mmol(1.5 litres STPD/min) were calculated from the regressions of ventilation and heart rate on oxygen consumption at each work load. Heart rate and oxygen uptake at the maximum work load achieved were also recorded. Normal limits for the cardiovascular and respiratory responses to exercise are given by Spiro, Juniper, Bowman & Edwards (1974).

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured on a low resistance spirometer (McKerrow, McDermott and Gilson, 1960) the best of three readings being taken (Freedman & Prowse, 1966).

Two separate studies were performed.

First study

In eight subjects FEV_1, FVC and the ventilatory responses to carbon dioxide and exercise were measured on three separate days 2h after administration of placebo, 80 mg propranolol or 100 mg metoprolol given double-blind in random order. Samples of venous blood were obtained 2h after the drug had been taken and plasma was subsequently analysed for metoprolol and propranolol levels (Ervik, 1975).

Second study

In order to study the effect of increasing plasma levels of the drugs, four subjects had ventilatory responses to CO_2 measured:

(i) before and 2h after either 80mg propranolol or 100 mg metoprolol given by mouth on a double-blind basis;
(ii) again 2h after a further 80 mg propranolol or 100 mg metoprolol, and
(iii) again 2h after a further 160 mg propranolol or 200 mg metoprolol.

Measurements were made on each subject with each drug on separate days.

In three subjects FEV_1 and FVC were also measured at each dose level and the ventilatory responses to exercise were measured in the same three subjects 2h after the last dose of β-adrenoceptor blocking drug.

Venous plasma samples withdrawn 2h after each dose of the drug were subsequently analysed for metoprolol or propranolol levels (Ervik, 1975).

P values for all comparisons were derived using the paired *t*-test, a *P* value of >0.05 being considered insignificant.

Table 1 Resting heart rate, FEV_1, FVC, slope (S_{CO_2}) and intercept (B_{CO_2}) of the CO_2 response line, and plasma levels of drugs (±s.d.) following placebo, propranolol 80 mg and metoprolol 100 mg in eight subjects.

	Placebo	*Propranolol 80 mg*	*Metoprolol 100 mg*
Resting heart rate (beats min^{-1})	66 ± 12	63 ± 15	63 ± 12
FEV_1 (ml)	4543 ± 461	4381 ± 407*	4431 ± 544
FVC (ml)	5612 ± 789	5512 ± 718	5543 ± 716
CO_2 responses			
Slope (S) (1 min^{-1} kPa^{-1})	16.31 ± 3.73	14.96 ± 4.11	13.83 ± 4.36
intercept (B) (kPa)	5.98 ± 0.62	5.81 ± 1.03	5.52 ± 1.57
Plasma levels (nmol l^{-1})	0	230 ± 166	350 ± 171

*$P<0.05$ for comparison with placebo

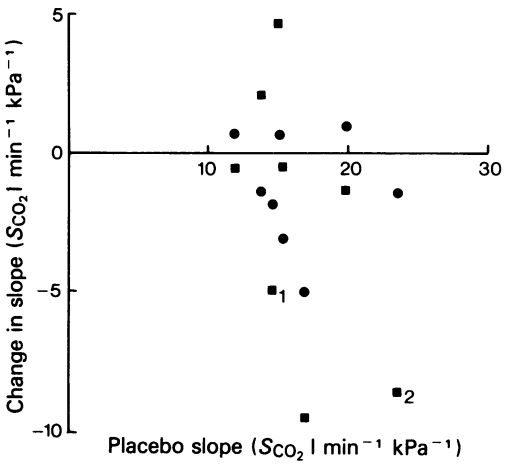

Figure 1 Individual changes in slope of the CO_2 response line following propranolol 80 mg (●) and metoprolol 100 mg orally (■) in eight subjects. Dose response studies in subjects 1 and 2 are shown in Figure 2.

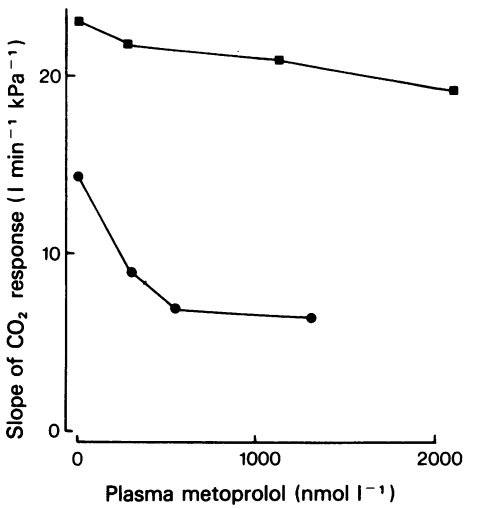

Figure 2 The relationship beween slope of the CO_2 response line and plasma metoprolol in the dose response study of two subjects (1 and 2 in Figure 1) who had previously shown depression of the CO_2 response slope following 100 mg metoprolol orally.

Table 2 Ventilatory and heart rate responses to progressive bicycle exercise 2h following placebo, propranolol 80 mg or metoprolol 100 mg in eight subjects (± s.d.)

	Placebo	*Propranolol*	*Metoprolol*
Maximum load (watts)	185 ± 21	177 ± 22	179 ± 23
O_2 uptake at max. load (mmol min^{-1})	106 ± 10	107 ± 19	105 ± 20
Maximum ventilation (l min^{-1} BTPS)	75.7 ± 14.6	71.6 ± 13.6	73.2 ± 15.3
Ventilation (l min^{-1} BTPS) at $\dot{V}_{O_2}$ 66.9 mmol min^{-1}	43.9 ± 5.7	44.3 ± 5.0	42.2 ± 4.2
Ventilation (l min^{-1} BTPS) at $\dot{V}_{O_2}$ 44.6 mmol min^{-1}	28.9 ± 6.7	26.7 ± 4.7	27.5 ± 3.5
Heart rate at maximum load (beats min^{-1})	166 ± 15	120 ± 13*	126 ± 26*
Heart rate (beats min^{-1}) at $\dot{V}_{O_2}$ 66.9 mmol min^{-1}	128 ± 13	103 ± 12*	103 ± 11*
Heart rate (beats min^{-1}) at $\dot{V}_{O_2}$ 44.6 mmol min^{-1}	106 ± 11	89 ± 9*	88 ± 10*

* $P < 0.001$ for comparison with placebo

Results

First study

Plasma concentrations of propranolol 2h after 80 mg propranolol orally were 230 ± 166 (s.d) nmol l^{-1} and of metoprolol 2h after 100 mg metoprolol orally 350 ± 171 (s.d.) nmol l^{-1}. Propranolol (80mg), but not 100 mg metoprolol, produced a small but significant fall in FEV_1 in the group, the largest individual fall being 300 ml. Significant differences from placebo for mean values of resting heart rate, FVC and the slope and intercept of the CO_2 response line were not found with either drug, although mean S_{CO_2} tended to fall with either drug (Table 1 and Figure 1).

Both drugs produced significant reductions in submaximal and maximal exercise heart rate but neither drug significantly affected submaximal or maximal exercise ventilation, oxygen uptake at maximum work load achieved or work load (Table 2).

Second study

No significant differences in mean parameters of the ventilatory response to CO_2 were found with increased plasma concentrations of propranolol and metoprolol in the four subjects studied although mean S_{CO_2} did fall with metoprolol (Table 3 and Figure 2) FEV and FVC did not change significantly with increasing plasma levels in the three subjects studied (Table 3).

The only exercise variables to change significantly with the higher plasma levels of both drugs in the three subjects studied were the heart rates at maximal and submaximal exercise (Table 4).

Discussion

When comparing our findings to those of Mustchin *et al.*, (1976), we noted that, as a group, their subjects had greater than average sensitivity to inhaled CO_2 whereas our group of subjects had average responses (Hirschman, McCullough & Weil, 1975). We therefore examined the possibility in our group of subjects that individual chages in sensitivity to CO_2 following β-adrenoceptor blocking drugs might be related to the pretreatment slope of the CO_2 response line and found no such relationship. Individual changes in the slope of the CO_2 response line after a single dose of each drug are shown in Figure 1. The changes in slope shown are generally small and occur in both directions. Only four decreases in slope were equal to or greater than 5 $min^{-1}kPa^{-1}$, three of these being after metoprolol. Two of the subjects (indicated in Figure 1) also took part in the dose response studies with metoprolol and propranolol. Subject 1 showed an identical decrease in slope following 100 mg metoprolol with a dose related further decrease (Figure 2). Subject 2 no longer showed a large decrease in a slope following 100 mg metoprolol and demonstrated only a minor dose-related effect (Figure 2). The two remaining subjects in the dose response study with metoprolol and all the subjects in the dose response study with propranolol demonstrated no striking change in S_{CO_2} and no dose related effect.

We have therefore been unable to confirm, as were

Table 3 Slope and intercept of CO_2 response line (± s.d.) with increasing plasma concentrations of propranolol and metoprolol in four subjects. FEV_1 and FVC in three of the four subjects.

Plasma propranolol concentration (*nmol* l^{-1})	*Slope of* CO_2 *response* (*l* min^{-1} kPa^{-1})	*Intercept of* CO_2 *response* (kPa^2)	FEV_1 (*ml*)	*FVC* (*ml*)
0	13.49 ± 4.77	5.80 ± 0.37	4643 ± 490	5743 ± 731
288 ± 137	13.12 ± 6.74	5.92 ± 1.01	4563 ± 586	5590 ± 905
570 ± 221	13.58 ± 5.31	6.24 ± 0.71	4380 ± 558	5690 ± 440
860 ± 148	15.40 ± 6.96	6.40 ± 0.64	4473 ± 551	5386 ± 903
Plasma metoprolol concentration nmol l^{-1})				
0	17.07 ± 4.53	5.96 ± 0.54	4570 ± 632	5773 ± 780
376 ± 102	15.33 ± 6.37	5.93 ± 0.82	4770 ± 308	5587 ± 507
798 ± 246	13.67 ± 6.92	5.89 ± 1.30	4430 ± 534	5360 ± 747
1038 ± 646	13.57 ± 5.60	6.13 ± 1.54	4380 ± 527	5487 ± 768

Table 4 Ventilatory and heart rate responses to progressive exercise, following administration of placebo, propranolol (80 mg or 320 mg) or metoprolol (100 mg or 400 mg) in three subjects.

		Propranolol		*Metoprolol*	
	Placebo	*80 mg*	*320 mg*	*100 mg*	*400 mg*
Maximum work load (watts)	178 ± 10	161 ± 19	150 ± 17	167 ± 17	161 ± 26
Oxygen uptake at maximum work load (mmol min^{-1})	96.5 ± 4.8	93.7 ± 7.9	86.1 ± 15.4	88.3 ± 5.9	92.3 ± 19.5
Maximum ventilation (1 min^{-1} BTPS)	71.7 ± 6.6	62.2 ± 4.7	52.7 ± 6.7	64.2 ± 12.7	60.7 ± 12
Ventilation (1 min^{-1} BTPS) at $\dot{V}_{O_2}$ 66.9 mmol min^{-1}	43.4 ± 1.5	41.5 ± 3.2	40 ± 1.7	44.7 ± 6.1	40.8 ± 2.6
Ventilation (1 min^{-1} BTPS) at $\dot{V}_{O_2}$ 44.6 mmol min^{-1}	28.3 ± 2.3	26.4 ± 2.3	27.7 ± 1.1	26.9 ± 0.5	26.5 ± 2.0
Maximum heart rate (beats min^{-1})	163 ± 15	113 ± 15***	99 ± 6***	112 ± 17***	102 ± 5***
Heart rate (beats min^{-1}) at $\dot{V}_{O_2}$ 66.9 mmol min^{-1}	132 ± 19	104 ± 14*	93 ± 8**	105 ± 12*	95 ± 6**
Heart rate (beats min^{-1}) at $\dot{V}_{O_2}$ 44.6 mmol min^{-1}	104 ± 12	88 ± 8*	81 ± 7*	88 ± 8*	83 ± 4*
Plasma levels (nmol l^{-1})	0	297 ± 176	880 ± 160	272 ± 239	860 ± 661

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

others in a brief report (Patrick & Pearson, 1978), Mustchin *et al.* s (1976) findings on the effect of propranolol given either as a single dose of 80mg or in incremental doses on the ventilatory response to inhaled CO_2. In general, our findings with metoprolol were similar.

We were also unable to demonstrate any significant effect of single doses of propranolol or metoprolol on ventilation at standard submaximal exercise levels of oxygen uptake. In view of the suggestion that CO_2 output might be the determinant of ventilation during exercise (Wasserman, 1978), we also examined the relationship between ventilation and CO_2 output following placebo, metoprolol and propranolol but were unable to demonstrate any consistent effects of the drugs. There is a consistent small fall in exercise ventilation (Table 4) following the higher doses of both drugs but this does not reach statistical significance. If there is an effect of β-adrenoceptor antagonists on exercise ventilation it would appear to occur only at moderate or higher levels of exercise and to require doses of drugs which are infrequently used in the clinical context.

The finding of a minor but significant decrease in FEV_1 following propranolol has been noted by other workers (Gayrard, Orehek, Grimaud & Charpin, 1975) as have the heart rate responses to β-adrenoceptor blocking drugs (Brown, Wasserman & Whipp, 1976; Reybrouck, Amery & Billiet, 1977). In spite of the marked fall in heart rate during exercise after these drugs exercise tolerance is unaffected for increases in stroke volume and oxygen extraction can compensate for the fall in heart rate (Reybrouck *et al.*, 1977).

We have been unable to demonstrate any consistent or significant effect of metoprolol or propranolol on the ventilatory responses of normal subjects to carbon dioxide or moderate graded exercise. If these findings are applicable to patients with chronic bronchitis, then neither metoprolol nor propranolol should be withheld on the grounds that they may cause worsening of CO_2 retention at rest or on exercise. A more important determinant of suitability for use in such patients will be the drug effect on airways obstruction (Skinner, Gaddie, Palmer & Kerridge, 1976; McGavin & Williams, 1979) and the present studies would favour metoprolol on that basis.

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