The effects of β -adrenoceptor blockade on breathing during progressive exercise in normal man

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1 We have studied the effects of single oral doses of 80 mg propranolol and 100 mg atenolol on breathing during progressive exercise in nine healthy men in a double-blind, placebo-controlled experiment. As judged by their effects on exercise heart rate significant levels of β -adrenoceptor blockade were achieved.

2 At the two lower levels of work rate (50 watts and 100 watts) minute ventilation on atenolol was lower than on placebo while at the highest level of work (200 watts) minute ventilation was higher on atenolol than on placebo. The regression of $\dot{V}_E$ on $\dot{V}_E$ placebo was 1.28 which is significantly different from unity ($P < 0.001$). The results with propranolol were more scattered and failed to reach the 5% level of significance.

3 Effects on the pattern of breathing are small but when minute ventilation is matched with placebo, atenolol results in larger tidal volumes and prolonged inspiratory and expiratory time.

4 These observations are discussed in relation to other work in the literature.

Keywords β -adrenoceptor blockade exercise ventilation tidal volume breath-time

Introduction

Previous work on the effect of β -adrenoceptor blocking drugs on the control of breathing in man has produced conflicting results. A summary of the results of several studies (Patrick & Pearson, 1980) concluded that β -adrenoceptor blocking drugs reduce the ventilatory response to inhaled carbon dioxide. Less attention has been given to hypoxic responses, but no effect was demonstrated by Heistad *et al.* (1972) or by Patrick *et al.* (1978).

The ventilatory responses to exercise are complex involving neural and humoral factors (Cunningham, 1963). Enhanced hypoxic drive during exercise (Cunningham *et al.*, 1968) may have as its basis increased sympathoadrenal activity. However, several studies have failed to demonstrate an effect on minute ventilation during graded exercise in normal subjects (Pearson, *et al.*, 1979; Leitch *et al.*, 1980; Petersen *et*

al., 1983; O'Neill *et al.*, 1984; McLeod *et al.*, 1985) whereas others have shown reductions in minute ventilation after propranolol at sub-maximal levels of exercise (Twentyman *et al.*, 1981; Violante *et al.*, 1984).

Catecholamines may influence respiratory control in a number of ways. In man, the effect of noradrenaline on breathing is mediated by the arterial chemoreceptors (Cunningham *et al.*, 1963a,b) similar results being obtained for both noradrenaline and adrenaline in the anaesthetised cat (Joels & White, 1968). However, other authors have shown in animals that, whereas a major component of the ventilatory response is mediated via the arterial chemoreceptors, a significant component is the result of direct effects on the central nervous system (Eldridge & Gill-Kumar, 1980; Winn *et al.*, 1979). Folgering (1980) concluded from his experiments with

β -adrenoceptor blocking drugs using cats that β -adrenergic mechanisms stimulating respiration exist within the brain stem. Finally, changes in bronchomotor tone can affect respiratory drive (Mills *et al.*, 1969).

We have studied the effects of two β -adrenoceptor blocking drugs on the control of breathing during exercise in normal non-asthmatic men. The drugs we used, namely, atenolol and propranolol differ in their effects on the central nervous system and the bronchial tree and so might be expected to influence differently the various mechanisms discussed above. The study was approved by the Ethical Committee of the Leeds Eastern Health Authority.

Methods

Nine normal non-asthmatic men (age range 22–35 years) were studied (Table 1). Each attended the laboratory on three occasions separated by at least 48 h having previously taken placebo, propranolol 80 mg or atenolol 100 mg 2 h earlier on an empty stomach. The drug administration was randomised and the subjects were informed what the experiments entailed when they volunteered.

Each experiment involved progressive exercise on a bicycle ergometer (Gould Corival 300) with 5 min at each of four levels of work rate; 50 watts, 100 watts, 150 watts and 200 watts. During the exercise inspiratory and expiratory flow was recorded using a pneumotachograph head (Fleisch No 3) attached to a pressure transducer (Ether Ltd Model UP1) the signal from which was amplified and converted into a digital signal using a 16 bit A–D convertor. The signal was fed into a Motorola computer using an OS9 operating system where it was integrated to give tidal volume (V_T) breath by breath. Inspiratory time (T_i), expiratory time (T_E) and total breath time (T_{TOT}) were measured from the points of

zero flow using an internal clock and minute ventilation ($\dot{V}_E$) was calculated breath by breath. Recordings were made during the last minute at each level of exercise. The relations between V_T , $\dot{V}_E$ and respiratory time (T_i , T_E and T_{TOT}) in the steady state in man have been described (Hey *et al.*, 1966; Cunningham & Gardner, 1977; Gardner, 1977). However, tidal volume and breath duration when studied on a breath-by-breath basis are influenced by mechanisms other than the Hey relation (Priban, 1963) the effects of which were minimised in these experiments by averaging the results for at least 20 consecutive breaths. Heart rate was recorded by palpation of the radial artery during the last minute at each work rate.

Statistical methods

Statistical analysis has been done using the Student's *t*-test for paired comparisons at each level of work. Departure of regression coefficients from unity has been tested by using a *t*-test (Bailey, 1959).

Results

The data from the 24 experiments are shown in Tables 2 and 3. Two subjects failed to achieve the 200 watt work rate after taking propranolol. The heart rate reductions at the highest work rate achieved in all three experiments for each subject was $52 \text{ beats min}^{-1} \pm 5.5$ (s.e. mean) or

Table 2 Paired comparisons at each work rate: atenolol–placebo (Differences shown $\pm$ s.e. mean)

Work rate (watts)	$\Delta \dot{V}_E$ (l min^{-1})
50	$-2.35 \pm 0.64^{**}$
100	$-3.37 \pm 1.24^*$
150	$+0.77 \pm 1.69$
200	$+8.41 \pm 3.17^*$

* $P < 0.05$; ** $P < 0.01$.

Table 3 Paired comparisons at each work rate: propranolol–placebo (Differences shown $\pm$ s.e. mean)

Work rate (watts)	$\Delta \dot{V}_E$ (l min^{-1})
50	-0.35 ± 2.09
100	$+7.08 \pm 5.12$
150	$+5.22 \pm 4.87$
200	$+7.16 \pm 6.35$

Table 1 Physical characteristics of the subjects

Subject	Age (years)	Height (cm)	Weight (kg)	FEV_1 (l s^{-1})	FVC (l)
1	26	178	70	4.99	6.41
2	30	182	81	5.33	6.87
3	26	183	71	4.69	6.35
4	27	175	72	4.29	5.33
5	30	175	70	4.17	5.17
6	24	178	75	4.35	5.42
7	24	185	78	5.10	6.55
8	35	174	65	3.85	5.23
9	24	176	75	4.30	5.70

31.9% on propranolol compared with placebo and 48 beats $\text{min}^{-1} \pm 5.4$ (s.e. mean) or 29.4% on atenolol compared with placebo. The heart rate on placebo was 163 beats $\text{min}^{-1} \pm 4.3$ (s.e. mean).

Effects on minute ventilation

Atenolol affects minute ventilation differently at low and at high levels of work. At 50 and 100 watts $\dot{V}_E$ is significantly depressed below the levels seen on placebo ($-2.35 \text{ l min}^{-1} \pm 0.64$ (s.e. mean) ($P < 0.01$) at 50 watts, and $-3.37 \text{ l min}^{-1} \pm 1.24$ (s.e. mean) ($P < 0.05$) at 100 watts). At work rates of 150 watts no significant difference is seen from placebo ($+0.77 \text{ l min}^{-1} \pm 1.69$ s.e. mean) and at 200 watts minute ventilation is significantly higher on atenolol than on placebo ($+8.41 \text{ l min}^{-1} \pm 3.17$ (s.e. mean) ($P < 0.05$)). The regression of $\dot{V}_E$ atenolol on $\dot{V}_E$ placebo (Figure 1) is 1.28 which is significantly greater than unity ($P < 0.001$) and in agreement with the above findings of depressed ventilation at lower work rates and enhanced ventilation at the highest work rate.

The results for propranolol are more scattered but no significant differences in ventilation from placebo are seen at the different work rates. The regression of $\dot{V}_E$ propranolol on $\dot{V}_E$ placebo (Figure 2) is 1.24 which shows the same trend as with atenolol but the result is not significantly different from unity at the 5% level in the case of propranolol because of the greater scatter in the data.

Figure 1 Regression of $\dot{V}_E$ atenolol on $\dot{V}_E$ placebo.

Figure 2 Regression of $\dot{V}_E$ propranolol on $\dot{V}_E$ placebo.

The pattern of breathing

Direct comparisons of the pattern of breathing can only be made at equal levels of minute ventilation. In the case of atenolol this occurs at the work rate 150 watts where it is found that on atenolol tidal volume is greater than on placebo ($+0.34 \text{ l} \pm 0.14$ (s.e. mean), $P < 0.05$), inspiratory time longer ($0.21 \text{ s} \pm 0.08$ (s.e. mean), $P < 0.05$) and expiratory time longer ($0.23 \text{ s} \pm 0.09$ (s.e. mean), $P < 0.05$). Total breath time is also longer than on placebo but fails to reach the 5% level of significance ($+0.31 \text{ s} \pm 0.17$ s.e. mean). There is a tendency for expiratory time also to be prolonged at 50 watts ($+0.21 \text{ s} \pm 0.14$ (s.e. mean)) and at 100 watts ($+0.34 \text{ s} \pm 0.14$ (s.e. mean), $P < 0.05$) but this is more difficult to interpret since atenolol also depresses minute ventilation at these two levels of work. Similar effects are not seen with propranolol.

Discussion

The principle finding of this paper is to confirm the results of Violante *et al.* (1984) that β -adrenoceptor blocking drugs reduce minute ventilation at submaximal but not at maximal exercise levels (above 150 watts). In our study the effects were seen most clearly with the cardio-selective drug atenolol. The results with propranolol showed the same trend but with more scatter, possibly because of the much greater variation in plasma levels known to occur follow-

ing single oral doses of propranolol than with atenolol. However, the fact that Violante *et al.* (1984) used propranolol supports the view that the effect in depressing ventilation is not related to cardioselectivity or lipid solubility. Twentyman *et al.* (1981) also found a tendency (not statistically significant) for $\dot{V}_E$ to be reduced during progressive exercise following propranolol but also found that the effect was time dependent, ventilation being depressed early in sub-maximal exercise but not as the steady-state is approached. In agreement with our findings Twentyman *et al.* (1981) also found that ventilation is increased after β -adrenoceptor blocking drugs at the highest levels of exercise.

The explanation of these observations is unknown. Twentyman *et al.* (1981) postulated that the depression in ventilation early in exercise may reflect delayed cardiovascular responses following β -adrenoceptor blocking drugs with reduced CO_2 flux to the lung. Petersen *et al.* (1983) similarly felt that any respiratory effects of the drugs were secondary to their cardiovascular effects. Changing the CO_2 flux to the lung alters the amplitude of the arterial Pco_2 oscillation until the steady-state is approached. Such oscillations are known to affect ventilation via the carotid arterial chemoreceptors (Goode *et al.*, 1969; Cunningham *et al.*, 1973). If different rates of cardiovascular adjustment to exercise on β -adrenoceptor blocking drugs are of importance in determining their respiratory effects, then this might explain the negative results reported by Pearson *et al.* (1979) where smaller more frequent step increments in load were used. Similarly small and frequent adjustments in exercise load were used in the negative study reported by Leitch *et al.* (1980). Although Violante *et al.* (1984) used only 25 watt increments they emphasize that their subjects were physically untrained unlike those of Pearson *et al.* (1979).

There are probably also direct effects of β -adrenoceptor blocking drugs on the chemical drive to breathing. The evidence is (as summarized by Patrick & Pearson, 1980) that propranolol has a small but consistent effect in depressing the ventilatory response to CO_2 inhalation. The effects are unlikely to be a result of direct action of the drugs on the arterial chemoreceptors since they occur when breathing CO_2 in oxygen (Cunningham *et al.*, 1965; Bernards *et al.*, 1966; Miller *et al.*, 1974). The available evidence is that β -adrenoceptor blockade does not affect the hypoxic drive to breathing (Patrick *et al.*, 1978) which is also against any direct effect on arterial chemoreceptors. On this basis a central action depressing either the medullary chemoreceptors or the respiratory centres seemed the

likely explanation for the effects of propranolol on CO_2 response. Whether such central effects can be applied to atenolol with its lower penetration of the central nervous system would seem more doubtful. It may be, therefore, that β -adrenoceptor blocking drugs are reducing some other source of respiratory drive during exercise, from muscle, for example, or from pulmonary afferents.

The different populations of pulmonary receptors produce different patterns of breathing when stimulated (Coleridge & Coleridge, 1986) and so we were interested to compare two β -adrenoceptor blocking drugs with different effects on the tracheobronchial tree. When minute ventilations are the same at 150 watts, atenolol produces a larger tidal volume with prolonged inspiratory and expiratory times. This pattern of breathing is what might be expected if airways resistance was increased during exercise on β -adrenoceptor blocking drugs (Otis *et al.*, 1950). The normal physiological response to exercise is one of airway dilatation (Warren *et al.*, 1984). Measurements of airway resistance during exercise are difficult to do, but using transpulmonary index as a measure of airway resistance, Warren *et al.* (1984) were able to show it was unaffected by β -adrenoceptor blockade in the form of 80 mg propranolol. Similar results are reported measuring specific airways conductance (Kagawa & Kerr, 1970). It seems unlikely, therefore, that our results can be explained by a simple increase in airways resistance during exercise, particularly as the effect is apparent with the more cardio-selective of the two drugs. More work is required to determine the basis for this effect of atenolol on breathing pattern.

Our finding that ventilation is increased by β -adrenoceptor blockade at the highest work rate agrees with the findings of Twentyman *et al.* (1981). These authors proposed greater anaerobiosis and metabolic acidosis as one possible mechanism but another might be an increased tendency to pulmonary venous congestion on β -adrenoceptor blocking drugs (Younes & Burk, 1985).

In summary, we publish findings which, taken with those of earlier authors, show that β -adrenoceptor blocking drugs do have small effects on the level of minute ventilation during progressive exercise. The effect is to depress ventilation at low levels of exercise and to stimulate it as maximal exercise levels are approached. Although our findings are clearest with the drug atenolol, the findings of earlier authors using propranolol suggest that this is not an effect related to cardioselectivity or lipid solubility. Effects on ventilatory pattern are small and this

area would be worthy of further study. A number of mechanisms have been proposed to account for these ventilatory effects of β -adrenoceptor blocking drugs which we have reviewed. It seems to us that effects on rate of cardiovascular adjustment and CO_2 transport (Brown *et al.*, 1976; Twentyman *et al.*, 1981; Petersen *et al.*, 1983) is the mechanism that is most likely on the present

evidence to explain the effects on submaximal minute ventilation.

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