Propranolol and the ventilatory response to hypoxia and hypercapnia in normal man

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Summary

1. The effect on respiration of a single dose of propranolol has been studied in normal subjects.
2. The degree of β-adrenoreceptor blockade was assessed in terms of the impaired heart-rate response to progressive exercise and the plasma propranolol concentration.
3. No effect of propranolol was demonstrated on either the ventilatory response to rebreathing CO₂ in hyperoxia, or the response to progressive isocapnic hypoxia. Simple indices of maximal expiratory flow (FEV₁₀₂% and PEFR) were also unchanged.
4. The absence of any effect of propranolol on the chemical control of breathing in man is discussed in relation to the conflicting literature.

Key words: β-adrenoreceptor blockade, chemoreceptors, hypercapnia, hypoxia, propranolol, respiration.

Abbreviations: FEV₁₀₂ forced expiratory volume in 1 s; FVC, forced vital capacity; PEFR, peak expiratory flow rate; Pet, partial pressure at end-tidal sampling.

Introduction

It has been known for some time that adrenaline stimulates respiration (Whelan & Young, 1953). Cunningham, Hey, Patrick & Lloyd (1963a) found that noradrenaline stimulated breathing in man by increasing the sensitivity to hypoxia without a direct effect on the sensitivity to carbon dioxide. This implied that there should be no effect of noradrenaline on breathing in man in hyperoxia, as was shown later by Cunningham, Lloyd & Patrick (1963b). In the anaesthetized cat Joels & White (1968) confirmed that both noradrenaline and adrenaline stimulated breathing via an effect on the carotid chemoreceptors, and that neither agent affected the response to inhaled carbon dioxide with high concentrations of oxygen.

Adrenaline affects both α- and β-adrenoceptors whereas noradrenaline has predominantly α-adrenoceptor activity in the cardiovascular system, with some β-receptor effects also. It is not clear which type of receptor is responsible for the stimulation of ventilation via the peripheral chemoreceptors by these catecholamines. Stone, Keltz, Sarkar & Singzon (1973) found that the respiratory responses to noradrenaline were not affected by phentolamine (an α-adrenoreceptor antagonist) or by propranolol (a β-adrenoreceptor antagonist), but Heistad, Wheeler, Mark, Schmid & Abboud (1972) found that propranolol partly attenuated the stimulation of respiration resulting from the infusion of noradrenaline, but that the response to hypoxia was unaffected. Mustchin, Gribbin, Tattersfield & George (1976) found that a single oral dose of propranolol impaired the response to carbon dioxide inhalation in hyperoxia in normal man, which led these authors to urge caution in the administration of propranolol to patients with chronic bronchitis. It is, of course, well known that β-adrenoreceptor-blocking drugs may have a bronchoconstrictor effect in patients with asthma.
The findings of Mustchin et al. (1976) suggest that propranolol might influence breathing by some mechanism other than antagonism of the predominantly α-adrenoreceptor effects of noradrenaline or of the mixed α- and β-adrenoreceptor effects of adrenaline, as both of these agents act on the carotid chemoreceptors, and only then in hypoxia. Mustchin et al. (1976) did not study hypoxia, which may be more important than hypercapnia as a drive to respiration in many patients with chronic bronchitis. We have now repeated similar studies to those of Mustchin et al. (1976) but extended them to include hypoxia.

Methods

In the first series we studied six men and two women, all healthy with normal lung function (Table 1). Both hypercapnic and hypoxic ventilatory drives were studied, each subject attending on two occasions, the first time having taken no drug and the second 2 h after taking 100 mg of propranolol (Inderal, ICI) orally on an empty stomach. Five of the subjects had no detailed knowledge of respiratory physiology and were unaware of the problem under investigation.

In addition to this open series, a double-blind study was conducted in which the response to CO₂ at high O₂ concentrations was determined by a rebreathing technique (Read, 1967). Breath-by-breath values of ventilation and tidal Pco₂ were obtained after the first minute from the recorder trace by using a Graf-Pen Digitizer (Sintrom Electronics), and analysed on a PDP-11 computer (Digital Equipment Corporation) with a FOCAL program. The correlation coefficient for the linear regression of ventilation on tidal Pco₂ was always greater than 0.81.

The response to hypoxia was measured with progressive hypoxia at constant end-tidal Pco₂ (Weil, Byrne-Quinn, Sodal, Friesen, Underhill, Filley & Grover, 1970). The subject first rebreathed through a dead space for 10–15 min until the ventilation and Pco₂ were stable. Sometimes, O₂-enriched gas was supplied at the end of the dead space to keep the initial end-tidal P0₂ above 12 kPa. After at least 10 min to stabilize, the subject was switched to a rebreathing bag, with a CO₂-absorber in a variable by-pass so as to keep the Pet,co₂ constant while the PI,co₂ fell steadily. Varying the volume of the initial dead space allowed the initial Pet,co₂ to be set at two levels about 1 kPa apart to provide sufficient data for analysis with minimum exposure to hypercapnia and hypoxia. Each hypoxia study lasted about 5 min.

Gas was sampled continuously from between the

### Table 1. Anthropometric data for the subjects used in the two series, and the plasma propranolol concentration at the end of the experiment (open series only)

<table>
<thead>
<tr>
<th>Series</th>
<th>Subject no.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>FEV₁₋₉ (l)</th>
<th>FVC (l)</th>
<th>PEFR (l/min)</th>
<th>Conc. of propranolol (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td>1</td>
<td>M</td>
<td>39</td>
<td>1.81</td>
<td>75</td>
<td>3.8</td>
<td>5.5</td>
<td>500</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M</td>
<td>30</td>
<td>1.88</td>
<td>86</td>
<td>5.5</td>
<td>7.5</td>
<td>580</td>
<td>46</td>
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<tr>
<td></td>
<td>3</td>
<td>M</td>
<td>42</td>
<td>1.79</td>
<td>82</td>
<td>4.6</td>
<td>6.2</td>
<td>510</td>
<td>89</td>
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<tr>
<td></td>
<td>4</td>
<td>F</td>
<td>28</td>
<td>1.61</td>
<td>51</td>
<td>3.6</td>
<td>4.1</td>
<td>450</td>
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<td>M</td>
<td>32</td>
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<td>72</td>
<td>5.0</td>
<td>6.1</td>
<td>545</td>
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<td></td>
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<td>F</td>
<td>25</td>
<td>1.74</td>
<td>73</td>
<td>4.1</td>
<td>4.8</td>
<td>380</td>
<td>129</td>
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<td>7</td>
<td>M</td>
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<td>1.81</td>
<td>81</td>
<td>5.7</td>
<td>6.5</td>
<td>707</td>
<td>57</td>
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<td></td>
<td>8</td>
<td>F</td>
<td>30</td>
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<td>70</td>
<td>4.4</td>
<td>5.0</td>
<td>585</td>
<td>49</td>
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<tr>
<td>Double-blind</td>
<td>9</td>
<td>F</td>
<td>20</td>
<td>1.73</td>
<td>68</td>
<td>3.9</td>
<td>4.2</td>
<td>405</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>M</td>
<td>21</td>
<td>1.82</td>
<td>71</td>
<td>4.6</td>
<td>5.3</td>
<td>620</td>
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<td></td>
<td>11</td>
<td>F</td>
<td>21</td>
<td>1.69</td>
<td>60</td>
<td>2.7</td>
<td>3.5</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>M</td>
<td>19</td>
<td>1.79</td>
<td>71</td>
<td>5.1</td>
<td>5.8</td>
<td>580</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>M</td>
<td>20</td>
<td>1.88</td>
<td>82</td>
<td>6.6</td>
<td>7.2</td>
<td>670</td>
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<tr>
<td></td>
<td>14</td>
<td>M</td>
<td>20</td>
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<td>66</td>
<td>3.9</td>
<td>5.0</td>
<td>550</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>M</td>
<td>21</td>
<td>1.81</td>
<td>77</td>
<td>4.9</td>
<td>5.8</td>
<td>740</td>
<td></td>
</tr>
</tbody>
</table>
flaps of a respiratory valve for analysis by an infrared CO₂ analyser (Uras) and from the expiratory side of the valve via a modified Rahn–Otis sampler (Taylor-Servomex model OA272). Both analysers were calibrated with gas mixtures analysed with a Lloyd–Haldane apparatus, and the gases from the analysers were returned to the breathing circuit. The lag in the response of both analysers was determined in each study. The gases were dried before measurement and corrected for saturated water vapour pressure at 37°C.

Ventilation was recorded by a Donald–Christie ‘bag-in-box’ attached to an Ohio 840 spirometer (Airco), giving a breath-by-breath record of tidal volume. Minute ventilation at each point was obtained from a running average of five breaths. The spirometer volume and end-tidal Po₂ and Pco₂ were recorded on a Grass multichannel recorder.

In the hypoxic studies blood was analysed for propranolol (Offerhaus & Van der Vecht, 1976). Progressive exercise on a bicycle ergometer assessed the β-adrenoreceptor blockade in terms of reduction in exercise heart rate. Exercise was increased by 25 W each 2 min with measurements over the second minute of each work load. The protocol used in the hypoxia experiments is shown in Table 2. The control experiments were identical except that no propranolol was given and no venous blood sample was taken.

Statistical methods

Comparisons of paired values in the same subject were made by Wilcoxon’s Signed Rank Sum test (Armitage, 1971), as the variables were unlikely to be normally distributed (Mustchin, 1977). Values are given as mean ± SD.

Results

Effectiveness of the β-adrenoreceptor blockade

The plasma propranolol concentration in venous blood taken at the end of the experiments in the open series was 80 ± 20 ng/ml (Table 1). The extent of the β-adrenoreceptor blockade induced by propranolol was shown by the cardiac frequency (fₑ) at a work-load which, in the control experiments, raised the frequency to 150 beats/min, the mean reduction in fₑ being 38 ± 7.4 beats/min or 25% (range 18–31%). The FEV₁,₀ and PEF of the subjects in the first series show that the mean difference due to propranolol was 0.9 ± 3.0% in FEV₁,₀ and 2.9 ± 17.4 I/min in PEF; neither difference was significant (Fig. 1).

Effects of propranolol

On CO₂ rebreathing in hyperoxia. In the open series, the slope of the CO₂-response line in hyperoxia was 20.9 ± 10.7 min⁻¹ kPa⁻¹ before propranolol and 18.0 ± 11.8 min⁻¹ kPa⁻¹ after. In the double-blind series with different subjects the corresponding values were 27.5 ± 12.4 and 28.4 ± 15.1 I min⁻¹ kPa⁻¹ (Table 3). These differences are not significant.

On the response to hypercapnia and hypoxia combined. Fig. 2 shows the method of analysis used. Ventilation is plotted against Pet,co₂ at two values of Pet,co₂ for the control and propranolol experiments separately. The vertical distance between the curves (e.g. a or b) represents the CO₂ responsiveness at a given Po₂. Pairs of Po₂ values chosen were identical in the two experiments in an individual subject, and were at least 2.7 kPa (mean 3.6 kPa) apart. The ratio of the two vertical distances, H, is a measure of the change in CO₂ response due to a change in Po₂. H therefore represents the sensitivity to hypoxia. Table 4 shows individual results for H. There is no significant difference between the control value for H, 1.67 ± 0.62, and the value after propranolol, 1.80 ± 0.72.

Discussion

β-Adrenoreceptor-blocking drugs are now widely used in clinical practice but, although the adverse
The finding of Mustchin et al. (1976) that propranolol reduced the sensitivity to CO₂ in hyperoxia implies that the drug acts on the central nervous system, as in man the contribution of the peripheral arterial chemoreceptors to the CO₂ ventilatory drive is negligible in hyperoxia (Lloyd, 1966; Cunningham, Lloyd, Miller & Young, 1965; Marsh, Lyen, McPhersen, Pearson & Cunningham, 1973). We cannot confirm the findings of Mustchin et al. (1976) and we can offer no satisfactory explanation for this. Both the heart rate in the progressive exercise text and the plasma propranolol measurements demonstrate that effec-
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TABLE 4. Effect of propranolol on \( H \), the ratio representing the subject's sensitivity to hypoxia

In Wilcoxon's Signed Rank Sum test, \( T^- \) (the sum of the ranks of the negative differences) equals 16. The critical value for 8 pairs at \( P = 0.05 \) is 3, so the null hypothesis cannot be rejected.

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>( P_O ) (kPa)</th>
<th>( H ) Before propranolol</th>
<th>( H ) After propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8.7</td>
<td>11.7</td>
<td>2.14</td>
</tr>
<tr>
<td>2</td>
<td>9.0</td>
<td>12.3</td>
<td>1.12</td>
</tr>
<tr>
<td>3</td>
<td>8.0</td>
<td>11.0</td>
<td>1.59</td>
</tr>
<tr>
<td>4</td>
<td>7.3</td>
<td>12.0</td>
<td>1.36</td>
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<td>5</td>
<td>6.7</td>
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<td>1.14</td>
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<tr>
<td>6</td>
<td>7.3</td>
<td>10.7</td>
<td>2.74</td>
</tr>
<tr>
<td>7</td>
<td>8.0</td>
<td>12.7</td>
<td>2.12</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
<td>12.0</td>
<td>1.42</td>
</tr>
<tr>
<td>Mean</td>
<td>—</td>
<td>—</td>
<td>1.67</td>
</tr>
<tr>
<td>SD</td>
<td>0.62</td>
<td>0.71</td>
<td></td>
</tr>
</tbody>
</table>

\( \beta \)-adrenoreceptor blockade was produced in our experiments. The variability of the \( CO_2 \) response within individuals is, however, substantial. In our hands the average difference between test/retest estimates of the \( \dot{V}/P_{co_2} \) slope on different days, irrespective of sign, is 27% of the mean value. In individual subjects the coefficient of variation of replicate determinations is 12%. Although we would be unlikely to detect small changes due to propranolol, we would have expected to see the 50% reduction in slope reported by Mustchin et al. (1976). Keltz, Mathur & Stone (1977) also found that infused propranolol had no significant effect on the slope of the \( CO_2 \)-response line in 20 adult men.

Sensitivity to hypoxia

Sensitivity to hypoxia is most satisfactorily measured as the expression \( A \) of the respiratory control equation

\[
\dot{V} = D(P_{co_2} - B)(1 + A/(P_O - C))
\]

of Lloyd, Jukes & Cunningham (1958). In this equation \( D \) represents the sensitivity to \( CO_2 \) in the absence of hypoxia, \( C \) the critical \( P_O \) at which the slope of the \( CO_2 \)-response line becomes infinite, and \( B \) the threshold \( P_{co_2} \). Full determination of the four variables with steady-state \( CO_2 \)-response lines at several different \( P_O \) values is a technique which usually requires an experiment lasting 3–4 h. Lengthy experiments of this kind are difficult to apply to single-dose drug studies when plasma concentrations are changing. The method of isocapnic progressive hypoxia used in our experiments allowed the respiratory data to be collected in less than half an hour and the whole experiment to be completed within an hour. The disadvantage of this method is that the two extremes of the rectangular hyperbola relating slope of the \( CO_2 \)-response line to \( P_{A,O_2} \) (below 7 kPa and above 13 kPa \( P_{A,O_2} \)) are not sufficiently well characterized to allow reliable estimates of \( A \) by iteration as described by Lloyd & Cunningham (1963) (Fig. 3). For this reason we employed the less-satisfactory method with the ratio, \( H \), of \( CO_2 \) responses at two \( P_O \) values, and found no change due to propranolol. \( H \) would be altered by changes in \( A \), \( C \) or \( D \) of the equation of Lloyd et al. (1958). However, we have evidence from the hypoxic \( CO_2 \)-rebreathing experiments discussed above that propranolol has no effect on \( D \), the \( CO_2 \) slope in hypoxia. The absence of any change in \( H \) makes it unlikely that propranolol has any significant effect on the ventilatory response to hypoxia. The variability of \( H \) is 43% between repeat estimates, illustrating the difficulty encountered by many authors in measuring sensitivity to hypoxia. Nevertheless, we would expect this method to have demonstrated the change in sensitivity caused by noradrenaline infusions (Cunningham et al., 1963a).

Other workers have also failed to show any effect of propranolol on the ventilatory response to hypoxia. Although Heistad et al. (1972) showed that propranolol prevented the stimulation of breathing by isoprenaline and noradrenaline in the presence of hypoxia, they found that it did not blunt the ventilatory response to hypoxia itself.
FIG. 2. Results from subject no. 7 plotted in the form of the hyperbolic relation between the slope of the CO₂-response line and the PO₂ (cf. Lloyd et al., 1958). A, C and D and their relation with H are discussed in the text.

Acknowledgments

We gratefully acknowledge the willing co-operation of our subjects, and the help of Mr P. Reilly of the Cripps Computer Centre. Mrs G. Kitchingman of the Department of Therapeutics performed the propranolol assays.

Keltz, Samortin & Stone (1972) failed to find an effect of propranolol on the resting ventilation of man breathing air but made no studies on subjects breathing hypoxic mixtures.

We conclude that the acute administration of propranolol does not modify the chemical control of breathing in normal man, and on this basis we assume that the drug can be safely given to patients with impaired respiratory drive, provided that there is no asthmatic component to their disease. We cannot comment on the effect of chronic administration.

FIG. 3. Results from subject no. 3 showing the calculation of H values. The subscript and superscript to H show the PO₂ values (kPa) at which estimates of CO₂ responsiveness were made. The ratio \( a/(b-4.9)/b/(6.2-4.9) \) = a/b represents the ratio of CO₂ responses at two PO₂ values for the control experiment (upper Figure), and similarly, a'/b' for the propranolol experiment (lower Figure). This ratio is called H. The difference in H values between the control and propranolol experiments gives an index of the effect of propranolol on the respiratory response to hypoxia.

Keltz, Samortin & Stone (1972) failed to find an effect of propranolol on the resting ventilation of man breathing air but made no studies on subjects breathing hypoxic mixtures.

We conclude that the acute administration of propranolol does not modify the chemical control of breathing in normal man, and on this basis we assume that the drug can be safely given to patients with impaired respiratory drive, provided that there is no asthmatic component to their disease. We cannot comment on the effect of chronic administration.

References


