

# Effect of acute and chronic beta-blockade on carbon dioxide sensitivity in normal man

P F HUTCHINSON AND R N HARRISON

*From the Faculty of Medicine, Southampton University Medical School, Southampton*

**ABSTRACT** The effect of beta-adrenoceptor antagonists on the respiratory response to carbon dioxide rebreathing was studied in eight normal subjects. Propranolol, atenolol, metoprolol, and placebo were given in random, double-blind fashion. Subjects were studied before each treatment period, after one dose, and after eight days of treatment with each drug. A rebreathing method was used to produce progressive hypercapnia and the respiratory response was assessed by measuring minute ventilation and maximum rate of change of inspiratory mouth pressure. Beta-blockade was assessed by the reduction in heart rate during steady state exercise on a cycle ergometer. There was no change in the respiratory response to carbon dioxide after a single dose or eight days treatment of any drug. All three active drugs produced a significant reduction in exercise heart rate. The forced expiratory volume in one second was not altered by any of the drugs.

Beta-adrenergic antagonists are used extensively in clinical practice but can produce airway narrowing in susceptible patients, particularly those with asthma.<sup>1</sup> The use of relatively cardioselective beta blockers may lessen the risk of bronchoconstriction but as some patients with airflow obstruction also have disordered ventilatory control,<sup>2</sup> it must be established whether the respiratory effects of beta-adrenergic blockade extend beyond changes in pulmonary mechanics.

Mustchin *et al*<sup>3</sup> observed that a single oral dose of propranolol markedly reduced the respiratory response to carbon dioxide rebreathing in normal volunteers, suggesting an effect on central control. Since a single dose of a non-cardioselective beta-blocker is unlikely to be given to patients at risk, we attempted to simulate the clinical situation by observing the effects of both acute and chronic beta blockade on ventilatory control. We used two widely prescribed cardioselective beta-blockers, atenolol and metoprolol, and compared them with a non-cardioselective drug, propranolol, in normal subjects. Metoprolol, a moderately lipid soluble drug, enters the central nervous system more readily than the water-soluble drug atenolol<sup>4 5</sup> so the two drugs will not necessarily have similar effects on respiratory control.

## Methods

Six male and two female volunteers were studied. Their mean age was 22.5 years (range 19–33 years). None gave any history of respiratory disease and all had normal spirometry. Two subjects smoked about 20 cigarettes per day. Informed consent was given and the study was approved by the local ethical committee.

Progressive hyperoxic hypercapnia was produced by a modified Read rebreathing method.<sup>6</sup> Carbon dioxide was measured by an infrared analyser (PK Morgan capnograph) which we showed to have a highly linear response between 5 and 11% CO<sub>2</sub>. A three-way valve enabled the subject to breathe from room air until he had settled on the mouthpiece and when ventilation was stable he was switched into a six-litre rebreathing bag initially containing a gas mixture of 5% CO<sub>2</sub> and 95% O<sub>2</sub>.

Ventilation was measured by displacement of air from a bag-in-box arrangement through an integrated pneumotachograph (Electrospirometer CS5; Mercury electronics). The maximum rate of change in inspiratory mouth pressure (dP/dt max) was measured simultaneously with ventilation. Subjects breathed through a low resistance spring-loaded two-way valve (Morgan 71522) which produced a transient and imperceptible occlusion at the start of each inspiration. Mouth pressure was

Address for reprint requests: Dr RN Harrison, Department of Respiratory Medicine, Level D, Centre Block, Southampton General Hospital, Tremona Road Southampton SO9 4XY.

measured by a pressure transducer (UPI; Pye Ether Ltd). The signal was amplified, electrically differentiated (Robec 1141 differentiation amplifier) and displayed on a high frequency response recorder (Mingograf 34; Elema-Schonander). The calibration procedure as described by Matthews and Howell,<sup>7</sup> was performed before each run.

Four-minute steady-state exercise tests were performed on an electrically braked cycle ergometer (Elema-Schonander). Work loads were chosen to give control exercise heart rates of more than 130 beats/minute in the last 30 seconds of exercise. Heart rate was determined from the electrocardiograph which was recorded using standard precordial leads and displayed on an ultraviolet recorder.

#### STUDY DESIGN

All subjects received an eight-day course of each of the following: propranolol 80 mg daily; metoprolol 200 mg daily; atenolol 100 mg daily; placebo. The order in which the courses were given was randomised for each subject, identical tablets of propranolol, atenolol, and placebo were used with a non-identical standard commercial preparation of metoprolol (Betoloc, Astra). The study was designed to be double-blind.

Subjects were made familiar with the rebreathing procedure before entering the formal study. They were studied at the same time of day on the first and last day of each course. No coffee, tea, or nicotine was allowed on study days and tablets were taken on an empty stomach.

On the first study day subjects rested supine for 15 minutes before performing a rebreathing run followed by spirometry and an exercise test. The first dose of the tablet was given and two hours later after a further period of rest the three tests were repeated in the same sequence. They then took the tablets for seven days and on the eighth day returned to the laboratory to repeat the three tests two hours after that day's dose. A two-week wash-out period was allowed between courses.

The first rebreathing run in each course before any treatment acted as control and was compared with the CO<sub>2</sub> responses after acute and chronic drug administration.

#### DATA ANALYSIS

All rebreathing traces were coded and read blind. Measurements of end-tidal carbon dioxide and minute ventilation were made every 20–30 seconds and the corresponding values of dP/dt max were taken as the mean of five breaths about a single CO<sub>2</sub> point. Minute ventilation was converted to

BTPS and end-tidal CO<sub>2</sub> expressed as partial pressure.

A linear regression of both minute ventilation and dP/dt max against PCO<sub>2</sub> was determined by the method of least squares. Only values corresponding to minute ventilation of greater than 20 l/min were analysed to avoid the "dog-leg" of the lower end of the response curve.

The slopes and x-intercepts of the regression lines after drug administration were compared with control values using Wilcoxon's signed rank test for paired data. Heart rates during exercise and spirometry were compared using Student's *t* test for paired data. The reproducibility of the method from day to day was assessed by measuring the coefficient of variation of the slopes of each subject's four control rebreathing runs.

#### Results

There were no serious side-effects from any of the drugs although all subjects were able to identify active treatment periods by an increase in muscle fatigue during the exercise tests. One subject withdrew for personal reasons before the completion of her final treatment period so the results for chronic metoprolol dosage are from seven subjects only.

Mean baseline data based on each subject's four control runs are shown in table 1. The comparison of control runs before starting a drug and subsequent runs after two hours and eight days of treatment is shown as pooled data for all subjects in table 2. No significant change was found in either the slope or x-intercept of ventilation or dP/dt max versus end-tidal CO<sub>2</sub> for any treatment.

The within-subject day-to-day variability in the response to CO<sub>2</sub> rebreathing was assessed as the coefficient of variation of the slopes and intercepts of each subject's four control runs. For the

Table 1 Mean baseline values of carbon dioxide sensitivity, FEV<sub>1</sub>, and exercise heart rate. The mean within-subject coefficients of variation (CV) are derived from each subject's four control runs

| Carbon dioxide sensitivity                      | Group $\pm$ 1SD mean | Mean within-subject CV (%) |
|---|----------------------|----------------------------|
| (i) Ventilation slope 1 min <sup>-1</sup> kPa*  | 17.58 $\pm$ 5.87     | 27.3                       |
| x-intercept† kPa                                | 5.25 $\pm$ 0.82      | 7.9                        |
| (ii) dP/dt max slope kPa sec <sup>-1</sup> kPa† | 0.96 $\pm$ 0.33      | 40.3                       |
| x-intercept kPa                                 | 5.12 $\pm$ 0.61      | 12.3                       |
| FEV <sub>1</sub>                                | 4.33 $\pm$ 0.64      |                            |
| Exercise heart rate                             | 148.7 $\pm$ 7.04     |                            |

\*1 kPa = 7.5 mmHg

†multiply by 1.3 to give cmH<sub>2</sub>O/sec/mmHg

‡ventilation or dP/dt max is plotted on the y-axis against end-tidal CO<sub>2</sub> on the x-axis.

Table 2 Effect of the acute and chronic administration of propranolol, metoprolol, atenolol, and placebo on carbon dioxide sensitivity, FEV<sub>1</sub>, and exercise heart rate. Values are the mean for the group\*

|                            |         | Propranolol | Metoprolol | Atenolol | Placebo |
|----------------------------|---------|-------------|------------|----------|---------|
| <b>Ventilation</b>         |         |             |            |          |         |
| slope                      | control | 19.33       | 17.15      | 16.34    | 17.53   |
|                            | 2 hours | 19.17       | 15.89      | 18.54    | 19.56   |
|                            | 8 days  | 18.20       | 16.58      | 17.09    | 21.09   |
| x-intercept                | control | 5.45        | 4.88       | 5.26     | 5.39    |
|                            | 2 hours | 5.49        | 5.19       | 5.61     | 5.09    |
|                            | 8 days  | 5.57        | 5.28       | 5.29     | 5.44    |
| <b>dP/dt max</b>           |         |             |            |          |         |
| slope                      | control | 1.01        | 0.94       | 1.02     | 0.87    |
|                            | 2 hours | 0.96        | 0.79       | 1.02     | 0.88    |
|                            | 8 days  | 0.72        | 0.74       | 0.82     | 0.94    |
| x-intercept                | control | 5.29        | 4.76       | 5.25     | 5.14    |
|                            | 2 hours | 5.13        | 4.83       | 5.06     | 4.77    |
|                            | 8 days  | 4.76        | 5.14       | 5.14     | 4.71    |
| <b>FEV<sub>1</sub></b>     |         |             |            |          |         |
|                            | control | 4.36        | 4.32       | 4.28     | 4.37    |
|                            | 2 hours | 4.31        | 4.23       | 4.27     | 4.35    |
|                            | 8 days  | 4.32        | 4.30       | 4.23     | 4.28    |
| <b>Exercise heart rate</b> |         |             |            |          |         |
|                            | control | 148.0       | 148.8      | 143.3    | 149.5   |
|                            | 2 hours | 114.6       | 111.5      | 111.8    | 147.8   |
|                            | 8 hours | 118.0       | 105.4      | 109.5    | 146.0   |

\*The eight day results with metoprolol are from seven subjects only. Full results are available from RNH.

ventilatory response slope this varied from 16.7% to 38.5% with a mean value of 27.3% (table 1).

There was a highly significant reduction in exercise tachycardia ( $p < 0.001$ ) for all subjects on active treatment at both two hours and eight days and no effect from placebo (table 2). No drug caused any significant change in FEV<sub>1</sub> (table 2) or vital capacity.

## Discussion

This study has shown that acute and chronic administration of the beta-antagonists propranolol, atenolol, and metoprolol did not change the respiratory response to carbon dioxide in normal volunteers.

The single dose studies are in accordance with the results of Patrick *et al*<sup>8</sup> who looked at propranolol and with Leitch *et al*<sup>9</sup> who studied metoprolol and propranolol. This is the first report of the effects of chronic dosage and we believe it to be relevant to clinical practice since it approximates to the way in which the drugs are actually given, and because the effects of chronic treatment are not necessarily the same as those of a single dose. For instance, pretreatment with atenolol may enhance its central nervous system uptake,<sup>4</sup> while the effects of the pharmacologically active metabolite of propranolol, 4-hydroxy-propranolol

may be important after a single dose but are not seen when the drug is given for more than five days.<sup>10</sup>

We were unable to repeat the observations of Mustchin *et al*<sup>3</sup> or support their conclusions that propranolol is a respiratory depressant. We are unable to explain this discrepancy although Mustchin<sup>11</sup> has himself emphasised the problems of using CO<sub>2</sub> rebreathing as a pharmacological tool, predominantly because of its poor within-subject reproducibility. Some of the factors contributing to this variability, such as the recent intake of coffee or the performance of the tests at different times of the day, can be controlled. Despite attention to such details we still found large spontaneous within-subject variation in CO<sub>2</sub> sensitivity between control runs, as illustrated by the large coefficients of variation (table 1). Studies during speech<sup>12</sup> and sleep<sup>13</sup> suggest that influences from higher centres modify the ventilatory response to inhaled carbon dioxide; these cannot be fully standardised from one run to the next so that problems of reproducibility may be insurmountable.

It is possible that small drug-induced changes in the response to CO<sub>2</sub> may have been obscured by the overall noise of our method but this would not have obscured a change of the magnitude seen by Mustchin *et al*.<sup>3</sup> They reported a mean reduction in the slope of ventilation versus end-tidal CO<sub>2</sub> of 46.6% after a single dose of propranolol.

We assessed respiratory centre activity by dP/dt max as well as minute ventilation since dP/dt max is less likely to be influenced by mechanical changes in the lungs produced by beta-adrenergic blockade. In fact none of the drugs produced a change in spirometry so the failure of the drugs to alter the ventilatory response to carbon dioxide was mirrored by an unchanged dP/dt max response (table 2). Our spirometry results are consistent with previous studies showing propranolol to have no effect on airway resistance in normal man,<sup>14 15</sup> and with the view that bronchomotor tone in normal subjects is not under the influence of beta-adrenergic activity. Our results differ from those of Johnson and Clarke<sup>16</sup> who showed that atenolol and metoprolol reduce the FEV<sub>1</sub> in normal man.

All our subjects showed a highly significant reduction in exercise tachycardia after both two hours and one week of active treatment, confirming beta-adrenergic blockade.<sup>17</sup> Although the study was designed to be double-blind, subjects were usually able to identify active treatment periods by the symptoms related to the exercise tests. The most common complaint was of increased lower

limb fatigue and muscle ache during heavy exertion, which occurred in at least one of each subject's three active treatment periods. This appeared to be more severe with the two selective beta-blocking drugs but we made no formal attempt to quantify symptoms and do not claim that the drugs were given in equipotent doses. There were no other side-effects of note.

Studies with metoprolol and propranolol<sup>18 19</sup> suggest that selective beta-blockers may be relatively safe in patients with airflow obstruction if there is no asthmatic component to their disease. As our results indicate that these drugs do not affect ventilatory control as assessed by CO<sub>2</sub> re-breathing in normal subjects, we believe it is now necessary to examine the effect of their chronic administration to patients with fixed airways obstruction and this work is now in progress.

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## References

- McNeill RS. Effect of a  $\beta$ -adrenergic-blocking agent, propranolol, on asthmatics. *Lancet* 1964; **2**:1101-2.
- Donald KW, Christie RV. The respiratory response to carbon dioxide and anoxia in emphysema. *Clin Sci* 1949; **8**:33-44.
- Mustchin CP, Gribbin HR, Tattersfield AE, George CF. Reduced respiratory response to carbon dioxide after propranolol: a central action? *Br Med J* 1976; **2**:1229-31.
- Bodin NO, Borg KO, Johansson R, Ramsay KH, Skanberg I. Tissue distribution of Metoprolol—(H<sup>3</sup>) in the mouse and the rat. *Acta Pharmacol Toxicol* 1975; **36**: suppl 5:116-24.
- Day MD, Hemsworth BA, Street JA. The central uptake of  $\beta$ -adrenoceptor antagonists. *J Pharm Pharmacol* 1977; **29**:52p.
- Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. *Australas Ann Med* 1967; **16**:20-32.
- Matthews AW, Howell JBL. The rate of inspiratory pressure development as a measure of responsiveness to carbon dioxide in man. *Clin Sci Mol Med* 1975; **49**:57-68.
- Patrick JM, Tutty J, Pearson JB. Propranolol and the ventilatory response to hypoxia and hypercapnia in normal man. *Clin Sci Mol Med* 1978; **55**:491-7.
- Leitch AG, Hopkin JM, Ellis DA, Merchant S, McHardy GJR. Effect of propranolol and metoprolol on the ventilatory responses to carbon dioxide and exercise. *Chest* 1978; **74**:342.
- Cleaveland CR, Shand DG. Effect of route of administration on the relationship between  $\beta$ -adrenergic blockade and plasma propranolol level. *Clin Pharmacol Ther* 1972; **13**:181-5.
- Mustchin CP. Carbon dioxide rebreathing and mouth occlusion pressure measurements. *JR Coll Physicians Lon* 1977; **12**:87-95.
- Phillipson EA, McClean PA, Sullivan CE, Zamel N. Interaction of metabolic and behavioural respiratory control during hypercapnia and speech. *Am Rev Respir Dis* 1978; **117**:903-9.
- Phillipson EA, Kozar LF, Rebuck AS, Murphy E. Ventilatory and walking responses to CO<sub>2</sub> in sleeping dogs. *Am Rev Respir Dis* 1977; **115**: 251-9.
- Richardson PS, Sterling GM. Effects of  $\beta$ -adrenergic receptor blockade on airway conductance and lung volume in normal and asthmatic subjects. *Br Med J* 1969; **3**:143-5.
- Tattersfield AE, Leaver DG, Pride NB. Effects of  $\beta$ -adrenergic blockade and stimulation on normal human airways. *J Appl Physiol* 1973; **35**: 613-9.
- Johnson N, McI, Clarke SW. The comparative effects of metoprolol and atenolol in healthy adults. *Acta Therapeut* 1978; **41**:147-51.
- McDevitt DG. The assessment of  $\beta$ -adrenoceptor blocking drugs in man. *Br J Clin Pharmacol* 1977; **4**:413-25.
- Tivenius L. Effects of multiple doses of metoprolol and propranolol on ventilatory function in patients with chronic obstructive lung disease. *Scand J Respir Dis* 1976; **57**:190-6.
- Sinclair DJM. Comparison of effects of propranolol and metoprolol on airways obstruction in chronic bronchitis. *Br Med J* 1979; **1**:168.