Thorax 1988;**43**:727–728

Morning-evening changes in airway responsiveness to methacholine in normal and asthmatic subjects: analysis using partial flow-volume curves

R W HEATON, M K GILLETT, P D SNASHALL

From the Department of Medicine, Charing Cross and Westminster Medical School, London

ABSTRACT In eight normal and eight asthmatic subjects airway responsiveness to methacholine was measured by means of partial flow-volume loops at 0800 and 1800 hours on the same day. Airway responsiveness was lower in the evening in both normal and asthmatic subjects.

Diurnal variation in airway calibre in asthmatic and non-asthmatic subjects is well documented.[1] De Vries *et al*[2] found a diurnal variation of histamine responsiveness in asthmatic subjects challenged repeatedly over 24 hours. We have measured airway responsiveness to methacholine in normal subjects at 0800 and 1800 hours, and compared the results with those obtained in asthmatic subjects.

Methods

We studied eight non-smoking subjects with no history of respiratory disease (seven male; mean age 30·5 years) and eight asthmatic subjects (five male; mean age 44 years). The asthmatic subjects had documented reversible airflow obstruction, but few symptoms. Subjects were asked to withhold all medication from 2200 h on the day before the study. All subjects gave their informed consent.

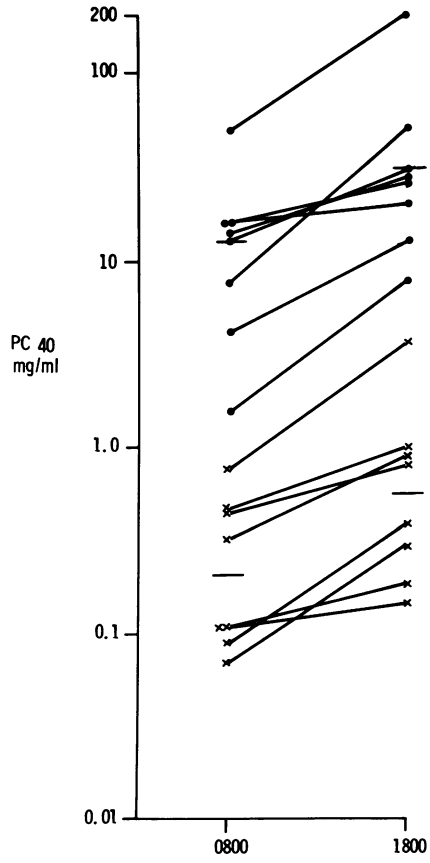
Airway responses were determined by measurement of maximal and partial flow-volume loops according to the method of Zamel.[3] FEV_1 was derived from the maximal loop and flow at 40% of vital capacity above residual volume from the partial expiratory loop ($\dot{V}_{40P}$). Methacholine was administered according to the method of Juniper *et al*,[4] doubling concentrations from 0·05 to 200 mg/ml being used.

Subjects attended the laboratory at 0800 and 1800 h on the same day. Repeated flow-volume manoeuvres were performed until stable values for FEV_1, forced vital capacity (FVC), and $\dot{V}_{40P}$ were obtained. Maximum values were taken as baseline readings. Doubling concentrations of methacholine were inhaled at five minute intervals until FEV_1 had fallen by at least 20% or the maximum concentration of methacholine had been given. Ninety seconds after each inhalation subjects performed a partial flow-volume loop manoeuvre followed immediately by a maximal flow-volume loop manoeuvre. FEV_1 and $\dot{V}_{40P}$ were plotted against log concentration of methacholine, and the concentrations of methacholine producing a 20% fall in FEV_1 (PC_{20}) and a 40% fall in $\dot{V}_{40P}$ (PC_{40}) were determined.

Logarithmic transformation of PC_{20} and PC_{40} values was carried out before analysis. Comparisons were made by paired *t* tests.

Results

There was no significant difference in baseline values of FEV_1 or $\dot{V}_{40P}$ between 0800 and 1800 h in either group of subjects (asthmatic subjects: mean (SD) FEV_1 2·47 (0·07) *v* 2·48



PC_{40} values (mg/ml) at 0800 and 1800 h on the same day in eight normal subjects (●) and eight asthmatic subjects (×). Horizontal bars indicate means of each group.

Address for reprint requests: Dr R W Heaton, Department of Medicine, Charing Cross and Westminster Medical School, London W6 8RF.

Accepted 21 March 1988

(0·24) l; $\dot{V}_{40P}$ 0·98 (0·55) *v* 0·98 (0·64) l/s; normal subjects: FEV_1 4·07 (0·45) *v* 3·95 (0·43) l; $\dot{V}_{40P}$ 3·05 (0·96) *v* 2·58 (0·64) l/s).

PC_{20} and PC_{40P} were significantly higher in both normal and asthmatic subjects at 1800 than at 0800 h. PC_{40P} rose in all the normal subjects (average rise 3·0 fold; $p < 0·001$) and in all but one of the asthmatic subjects (average rise 2·7 fold; $p < 0·001$) (figure). We could obtain a PC_{20} value in only five of the eight normal subjects in the morning and in only one in the evening. The mean maximum fall in FEV_1 in this group was 23% (13·6% at 0800 and 11% at 1800 ($p < 0·005$). PC_{20} values rose in six of the eight asthmatic subjects (average rise 1·5 fold; $p < 0·02$).

Discussion

Airway responsiveness to methacholine was lower (PC values higher) at 1800 than at 0800 h in the absence of any significant change in baseline airway calibre as measured by FEV_1 or PC_{40P}. These results are in agreement with those of previous studies.[2 5 6]

The magnitude of the changes in bronchial responsiveness was similar in the two groups, PC_{40P} being three times as high in the evening as in the morning in both normal and asthmatic subjects. The mechanism by which the response to methacholine changes during the day appears therefore to be related to normal regulation of bronchial smooth muscle function rather than any pathological state. The finding of a similar decrease in cough response to citric acid during the day[7] implies an overall down regulation, both motor and sensory, of airway responsiveness during the course of the waking day.

When bronchial challenge testing is used for diagnostic purposes[8] care must be taken to ensure that the time of day at which subjects are assessed is considered when results are interpreted. The figure shows that our least sensitive asthmatic subject showed a variation in PC_{40} that would lift him in the evening test into the range of our subjects who were normal at 0800 h. Studies attempting to assess the prevalence of bronchial hyperresponsiveness in a population that use the same arbitrary cut off point, irrespective of when the subjects were tested,[9] may produce misleading results with "intermediate" reactors possibly crossing the cut off line, depending on whether they were tested in the morning or in the evening.

In conclusion, changes in bronchial responsiveness during the waking day occur in normal and asthmatic subjects. When sensitive tests, such as the $\dot{V}_{40P}$, are used to assess responsiveness this variation is of considerable magnitude and necessitates care in the interpretation of the results of bronchial challenge testing.

References

1 Clark TJH, Hetzel MR. Diurnal variation of asthma. *Br J Dis Chest* 1977;**71**:87–92.

2 de Vries K, Goei JT, Booy-Noord H, Orie NGM. Changes during 24 hours in the lung function and histamine hyperreactivity of the bronchial tree in asthmatic and bronchitic patients. *Int Arch Allergy* 1962;**20**:93–101.

3 Zamel N. Partial flow volume curves. *Bull Eur Physiopathol Respir* 1984;**20**:471–5.

4 Juniper E, Frith PA, Dunnett C, Cockcroft DW, Hargreave FE. Reproducibility and comparison of responses to inhaled histamine and methacholine. *Thorax* 1978;**33**:705–10.

5 Reinberg A, Gervais P, Morin M, Abulher C. Circadian rhythms in the threshold of bronchial response to acetylcholine in healthy and asthmatic subjects. In: Schering LE, Halberg F, Pauly JE, eds. *Chronobiology*. Tokyo: Igaku Shoin, 1974:174–7.

6 Gervais P, Reinberg A, Gervais C, Smolensky M, De France O. Twenty-four hour rhythm in the bronchial hyper-reactivity to house-dust in asthmatics. *J Allergy Clin Immunol* 1977;**59**: 207–13.

7 Pounsford JC, Saunders KB. Diurnal variation and adaptation of the cough response to citric-acid in normal subjects. *Thorax* 1985;**40**:657–61.

8 Parker CD, Bilbo RE, Reed CE. Methacholine aerosol as a test for bronchial asthma. *Arch Interm Med* 1965;**115**:452–8.

9 Woolcock AJ, Peat JK, Salome CM *et al*. Prevalence of bronchial hyper-responsiveness and asthma in a rural adult population. *Thorax* 1987;**42**:361–8.