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

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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. De Vries et al 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. FEV₁ was derived from the maximal loop and flow at 40% of vital capacity above residual volume from the partial expiratory loop (V₄₀p). Methacholine was administered according to the method of Juniper et al, 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 FEV₁, forced vital capacity (FVC), and V₄₀p were obtained. Maximum values were taken as baseline readings. Doubling concentrations of methacholine were inhaled at five minute intervals until FEV₁ 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. FEV₁ and V₄₀p were plotted against log concentration of methacholine, and the concentrations of methacholine producing a 20% fall in FEV₁ (PC₁₀) and a 40% fall in V₄₀p (PC₄₀) were determined.

Logarithmic transformation of PC₁₀ and PC₄₀ values was carried out before analysis. Comparisons were made by paired t tests.

Results

There was no significant difference in baseline values of FEV₁ or V₄₀p between 0800 and 1800 h in either group of subjects (asthmatic subjects: mean (SD) FEV₁, 2.47 (0.07) v 2.48

PC₄₀ 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.
(0-24); \( I_{ap} \) 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; \( I_{ap} \) 3-05 (0-96) v 2-58 (0-64) l/s.

PC\(_{20}\) and PC\(_{ap}\) were significantly higher in both normal 
and asthmatic subjects at 1800 than at 0800 h. PC\(_{ap}\) 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\(_{ap}\). These results are in agreement with those of previous 
studies.\(^5\)\(^6\)

The magnitude of the changes in bronchial responsiveness 
was similar in the two groups, PC\(_{ap}\) 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\(^4\) 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,\(^*\) may produce misleading results with "inter-
mediate" reactors possibly crossing the cut off line, depend-
ing 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 \( I_{ap} \), 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 
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 
3 Zamel N. Partial flow volume curves. Bull Eur Physiopathol Respir 
4 Juniper E, Firth PA, Dunnett C, Cockcroft DW, Hargrave FE. 
Reproducibility and comparison of responses to inhaled 
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, 
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 
8 Parker CD, Bilbo RE, Reed CE. Methacholine aerosol as a test for 
hyperresponsiveness and asthma in a rural adult population. 
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