

Absence of diurnal variability of airway reactivity and hypoxic ventilatory drive in adolescents with stable asthma

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Background: Symptoms from asthma are often prominent at night. In adults significant circadian variation has been shown with reduced peak expiratory flow rates and increased bronchial reactivity to methacholine in the early morning hours. Because adolescence is the age group with the greatest increase in asthma-related deaths in the 1980s, we hypothesized that adolescents might be susceptible to circadian variation of airway reactivity.

Objective: We sought to measure circadian variation of reactivity to methacholine (PC₂₀) and hypoxic ventilatory drive (HVD), both of which would accentuate asthma that occurs at night and may predispose to death.

Methods: Sixteen children with asthma of various severity, aged 9 to 18 years, were studied at 4 PM and again at 4 AM to define circadian variation in FEV₁, PC₂₀, and HVD. Eleven children were studied on a second day 4 to 10 weeks after the first study.

Results: There was no systematic variation between 4 PM and 4 AM for FEV₁ ($P = .69$), PC₂₀ ($P = .94$), or HVD ($P = .47$). Six of the 16 children had PC₂₀ values that were greater than 2-fold different between 4 PM and 4 AM; 3 of these were more reactive (requiring less methacholine) at 4 PM, and 3 were more reactive at 4 AM. At the second study, results were similar, with no systematic variation. Diurnal variability for PC₂₀ was not consistent over the 2 study days, and at the second study all children with diurnal variability were more reactive at 4 PM.

Conclusion: These data on airway reactivity, HVD, and other measures modulated by cholinergic neural mechanisms do not identify any systematic diurnal variation that would place an adolescent at risk for nighttime problems with asthma. (*J Allergy Clin Immunol* 1999;103:804-9.)

Key words: Asthma, adolescence, airway reactivity, cholinergic tone, diurnal variability

Severe attacks of asthma that result in death most commonly occur at night.¹⁻⁵ Mortality caused by asthma increased from the late 1970s into the 1990s.⁶ Although death rates have increased in all age groups, adolescents are the group with the largest percentage increase.⁶ The association between asthma deaths and sleep is present for both adults^{1,2,5} and children.^{3,4}

Nocturnal symptoms from asthma occur commonly in adults. Turner-Warwick⁷ conducted a survey of 7729

Abbreviations used

HVD: Hypoxic ventilatory drive
NAEPP: National Asthma Education and Prevention Program
RSA: Respiratory sinus arrhythmia

asthmatic patients in the United Kingdom. Ninety-four percent reported at least 1 nighttime awakening a month. Thirty-nine percent awoke every night. Adults with asthma have been studied extensively and have been shown to have large circadian swings in peak expiratory flow rates, with a nadir in the early morning hours. This variability occurs even during periods of overall stability of asthma. For example, Bagg and Hughes⁸ found a morning decrease in peak expiratory flow rates in 30 of 40 subjects with stable asthma. Similarly, bronchial reactivity to methacholine has circadian variation, with a marked increase in reactivity at 4 AM when compared with reactivity at 4 PM.^{9,10} Abnormal responsiveness to hypoxia that accompanies severe asthma is another factor that has been hypothesized to play a role in asthma death, particularly as related to sleep. Olson and Saunders¹¹ studied 2 adults who had been resuscitated from respiratory arrest caused by asthma. Both patients had significantly lower responses to hypoxia than 7 normal control subjects. Kikuchi et al¹² also reported that adults with a history of respiratory failure from asthma had decreased responsiveness to hypoxia.

Although most patients who die from asthma are older adults, adolescents are the age group with the greatest increase in deaths in the 1980s.⁶ Adolescents are undergoing rapid changes in levels of hormones related to sexual maturation. We hypothesized that adolescents might be susceptible to circadian variation of airway reactivity and hypoxic ventilatory drive (HVD). This study was designed to test the hypothesis that diurnal variation of airway reactivity in adolescents correlates with maturation; specifically we hypothesized that more reactivity will occur during periods of change in maturation. In addition, increased reactivity in the airways may reflect an increase in vagal tone more generally. Because HVD is mediated in part by vagal nerve mechanisms, it may have diurnal variation correlated with airway reactivity.

METHODS

Subjects

Sixteen children, aged 9 to 18 years, were recruited from patients followed in the clinics of the Division of Allergy and Pulmonary Medicine at St Louis Children's Hospital. All had asthma by the

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standard criteria of the National Asthma Education and Prevention Program (NAEPP).^{13,14} Inclusion criteria also included the ability to perform methacholine challenge testing¹⁵ at 2 time points within a 24-hour period, 1 during the afternoon and 1 at night. The study was approved by the Washington University School of Medicine Institutional Review Board.

Asthma was stable as defined historically by (1) no change in medication requirements and no increase in symptoms over baseline in the month before study and (2) reproducible spirometry without a fall during repeated forced vital capacity maneuvers both at baseline and after inhalation of nebulized normal saline on the day of the study.

Overall severity of asthma was categorized by the NAEPP scoring system, which is based on medications required to maintain control of asthma chronically.¹⁴ Nocturnal prominence of asthma was determined from the history of the pattern of asthma over the past year, which was obtained from the mother. Although seasonality of asthma symptoms was documented historically in some children, the children were not necessarily studied in ($n = 3$) or out ($n = 13$) of their allergy season.

Of the 16 children studied, 11 were studied a second time to determine whether there was a change in diurnal variability in airway reactivity over intervals ranging from 4 to 10 weeks.

Protocol

Subjects were admitted to the Clinical Research Center in the early afternoon. Maturation was assessed by Tanner staging. Theophylline, inhaled and nasal steroids, and cromolyn sodium were continued as prescribed. On the day of admission, a dose of β -agonist was allowed only in the early morning. Each subject was interviewed for history of allergy, nocturnal asthma, and asthma severity, and each received a physical examination. A Holter monitor was then placed by 2:30 PM, and electrocardiographic monitoring was continued for the duration of the study. After placement of the Holter monitor, there was a 30-minute rest period, and then quiet activities were resumed.

At 4 PM, the subjects were taken to the pulmonary function laboratory to participate in an HVD study. Immediately after the HVD study, the subject was challenged with methacholine. The child was then returned to the clinical research unit. At 9 PM, spirometry was performed before administration of nighttime medication. At 3:30 AM, the child was awakened, and spirometry was performed. The subject then returned to the pulmonary function laboratory at 4 AM for a second HVD study and methacholine inhalation challenge as outlined above.

Assessment of HVD was performed by using techniques similar to those previously described by Weil and colleagues^{16,17} and Rebuck and Read.¹⁸ Earphones playing a favorite tape were used to distract the child's attention away from the monitoring devices during the study. The child breathed through an unidirectional high-volume closed circuit. The loop was initially filled with room air. It incorporated a CO₂ scrubber that could be dialed in or out of the circuit as necessary to maintain an end tidal CO₂ of 40 mm Hg as rebreathing into the closed circuit proceeded (end tidal CO₂ was monitored with a probe placed at the proximal airway and measured continually with an IL 200 infrared CO₂ monitor). All physiologic parameters were recorded on separate channels of a Gould (RS 3800) 8-channel recorder. Oxygen saturation and heart rate were monitored continually with a probe placed on the finger by means of a Nellcor 200 oximeter. Flows were measured by means of a Rudolph Linear pneumotach (Model 3813; linear flow range, 0 to 800 L/min) and a Validyne differential pressure transducer (Model MP45-871; range, ± 2 cm H₂O to ± 500 mm Hg differential) integrated to volume (Gould integrator amplifier), accumulated, and

TABLE I. Subject characteristics

No. of subjects	16
Mean age (y)	12.7 $\pm$ 2.4 (range, 9 to 18)
Girls/boys	5/11
White/black	10/6
Tanner stage (no. of subjects)	
1	6
2	0
3	6
4	3
5	1
Asthma severity (no. of subjects)	
Mild intermittent	2
Mild persistent	7
Moderate persistent	4
Severe persistent	3
History of nocturnal wheeze (no. of subjects)	
Yes	10
No	6
Medications (no. of subjects)	
β_2 adrenergics	16
Theophylline	10
Cromolyn	12
Inhaled steroids	10
Oral steroids	1

recorded with real time tracings of expiratory volume in 6-second intervals. The saturation at the end of each 6-second interval was plotted against the expiratory volume for the interval. The best fit slope was calculated for each HVD study by using a linear regression analysis. HVD was defined as $V_e/6\text{sec}/\text{saturation}$. The end point for the study was a drop in the child's oxygen saturation to 65% or when the child voluntarily came off the mouthpiece.

Methacholine challenge testing was performed by using the 2-minute tidal breathing technique described by Cockcroft et al.^{19,20} The flow rate to the Wrights nebulizer was adjusted to 7.5 L/min, which was previously determined to deliver a volume of 0.13 mL/min. After baseline, spirometry was obtained, and normal saline was administered by nebulization. The postnormal saline FEV₁ values had to be within 10% of the baseline values for the study to continue. Three spirometry were obtained, and the FEV₁ values were averaged to provide the basis for comparison of the effect of the methacholine. Methacholine was started at 0.03 mg/mL and doubled with each successive test dose. Spirometry was performed at 30 seconds and again at 90 seconds after inhalation of each dose. The lesser of the child's FEV₁ values was noted, and the challenge continued until FEV₁ dropped 20% or until the maximal dose of 16 mg/mL was inhaled. A noncumulative dose-response curve was constructed, and a PC₂₀ was calculated by linear interpolation of the last 2 points on the curve.

Vagal tone was estimated by the amplitude of respiratory sinus arrhythmia (RSA). This amplitude, as operationalized by Porges vagal tone measure,* is commonly observed as an increase in heart rate during inspiration and a decrease during expiration. Because

*This method converts heart periods into time-based data by sampling in successive 200-millisecond intervals. After baseline, drift and periodicities of heart rate slower than RSA were removed with a 21-point moving polynomial, the remaining data were processed by a band-pass filter to extract the variance of heart period within the frequency band of spontaneous breathing in adolescents and preadolescents (ie, 0.24 to 1.04 Hz or 14 to 62 breaths/min), and the natural logarithm of the band-assessed variance was calculated and used as the estimate of vagal tone (V).

TABLE II. Measures of reactivity and cholinergic tone on day 1 and diurnal variability*

	n	4 PM			4 AM			Diurnal variability		
		Mean†	Median	25th-75th percentile	Mean	Median	25th-75th percentile	Estimate ± SEM of log values	Observed effect size‡	95% confidence interval
FEV ₁ §	16	101.73	103.00	94-114	100.01	103.5	89-113	-0.005 ± 0.025	0.99	0.95-1.05
PC ₂₀ §	16	0.94	0.88	0.39-2.18	0.90	0.85	0.31-3.45	0.242 ± 0.234	1.27	0.79-2.03
HVD§	13	0.017	0.018	0.014-0.023	0.014	0.016	0.008-0.025	-0.99 ± 0.305	0.91	0.49-1.67
Vagal tone§	12	6.29	6.5	5.6-7.3	7.2	7.4	7.1-7.8	0.063 ± 0.046	1.07	0.97-1.17

*Computations based on mixed model with all available data (4 AM and 4 PM for both day 1 and day 2).

†Means are back transformed from the natural logarithmic transformations.

‡Observed effect size = (mean at 4 AM - mean at 4 PM)/standard deviation of differences.

§Units of measurement: FEV₁, mean percent predicted; PC₂₀, mean; HVD, V_e/6 sec/saturation; vagal tone, V.

the degree of heart rate change caused by respiratory activity is dependent on the vagal efferent input to the sinoatrial node, RSA is believed to provide a valid and reliable estimate of vagal responsiveness by means of neural control of the heart.²¹ Thirty-minute epochs starting at 3 PM and 3 AM were extracted from the Holter recording of electrocardiography for analysis. At 3 PM, the children were engaged in quiet activities after admission to the study, and at 3 AM, they were sleeping. The beginning of each of these periods preceded methacholine challenge by 60 minutes. The individual heart periods, defined from the peak of the R-wave for each cardiac cycle and sequential R-wave timed to the nearest millisecond, were examined for nonphysiologic artifact, artifact was edited, and the resulting data was processed by using Porges' method^{22,23} to provide an estimate of the amplitude of the RSA. Vagal tone was calculated for sequential 10-second epochs, and summary measures of these epochs were used in the statistical analyses.

Data quantification and statistical analysis

Summary statistics (eg, mean, median, and interquartile range) were computed for PC₂₀, FEV₁, HVD, and vagal tone for each subject for the 4 PM and 4 AM periods of study (for vagal tone, 3 PM and 3 AM). Because the distributions were nonnormal, a natural logarithmic transformation was computed for each subject's measures. These transformed values were used in all analyses, but values were back transformed for presentation purposes. Correlations and *t* tests were performed to compare the 4 PM and 4 AM measures for those subjects studied on day 1 and separately for those studied on day 2 and finally across the 2 study days for each time period. The difference and direction of difference between values measured at each time period were also computed, compared across subjects and study days, and analyzed with respect to demographic and clinical characteristics by using Pearson correlations, repeated-measures ANOVA, or Fisher's exact tests. In addition, for PC₂₀, subjects were characterized as having significant diurnal variability if their values of PC₂₀ measured at 4 PM and 4 AM were different from one another by 2-fold or more, calculated separately for the 2 days of study. With a sample size of 16 and an α value of .05, the study had a power of 0.80 to detect a systematic doubling in PC₂₀ from 4 PM to 4 AM.

RESULTS

Subject characteristics

The mean age of the 16 subjects was 12.7 ± 2.4 years and ranged from 9 to 18 years (Table I). Ten of the 16 children had a history of nocturnal prominence of asthma symptoms. Asthma was categorized as severe and persistent in 3 children, moderate and persistent in 4 children, mild and persistent in 7 children, and mild and intermittent in 2 children. Boys tended to be younger than girls

(11.9 ± 1.8 vs 14.4 ± 2.8 years, $P = .05$) but with asthma of similar severity (NAEPP scores of 2.4 ± 0.9 vs 2.8 ± 1.1 , $P = .42$). African American subjects had a more prominent history of nocturnal wheeze ($\chi^2 = 5.8$, $P = .02$) but not more severe disease ($P = .30$).

On admission to the Clinical Research Center, asthma was stable, and airway obstruction was mild, with FEV₁ values at 4 PM ranging from 71% to 122% of predicted value (mean, 102%). FEV₁ was lower in subjects with more severe asthma ($r = -0.49$, $P = .02$) and with a history of prominent nocturnal wheeze (97 ± 13 vs 113 ± 12 , $P = .04$). Methacholine reactivity (PC₂₀) at 4 PM was in the severe to mild range, with values ranging from 0.19 to 8.7 mg/mL (mean, 0.94 mg/mL). Mean HVD was 0.017 V_e/6 sec/saturation, and mean vagal tone was 6.3 V. The subjects did not have nocturnal asthma during either day of study as there were no asthma signs or symptoms during sleep or on awakening. The mean, median, and interquartile range for each dependent variable are shown in Table II.

Diurnal variability of FEV₁

There was a significant correlation between FEV₁ values at 4 PM (mean, 101.73% predicted) and 4 AM (mean, 100.01%) on day 1 ($r = 0.71$, $P = .002$). Furthermore, there were no significant differences in mean values at these 2 times ($P = .69$). Only one subject's mean value at 4 AM was greater than 10% lower than that at 4 PM; 2 subjects' mean values at 4 AM were greater than 10% higher than those at 4 PM (Fig 1, A).

For the 11 subjects studied a second time (data not shown), there was a strong correlation between the 4 AM (mean, 102.5% of predicted value) and 4 PM (mean, 101.1%) values ($r = 0.93$, $P = .0001$). Again, there were no significant differences between them (103.1 [4 PM] vs 104.3 [4 AM], $P = .57$). Furthermore, mean values at 4 PM in the first study were highly correlated with mean values at 4 PM in the second study ($r = 0.84$, $P = .001$) and similarly at 4 AM for both studies ($r = 0.77$, $P = .006$). The overall estimate of the effect of diurnal variability, using both day 1 and day 2 data, was 0.99 and not significant (Table II).

Diurnal variability of PC₂₀

During the first day of study, mean values of PC₂₀ at 4 PM (mean, 0.94) and at 4 AM (mean, 0.90) were signifi-

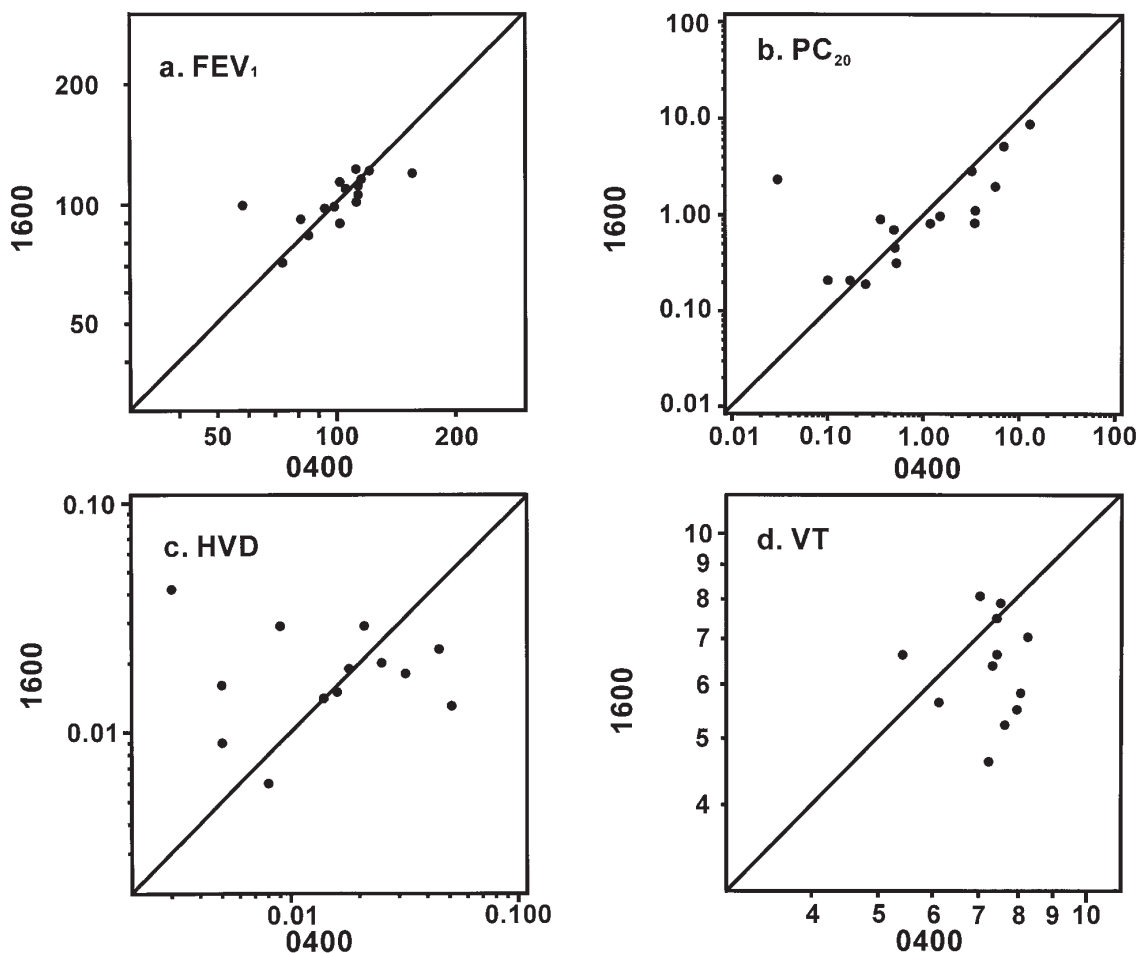


FIG 1. Scatterplot of diurnal variability of FEV₁ (a), PC₂₀ (b), HVD (c), and vagal tone (VT) (d). Raw mean values are plotted on natural logarithmic scale. For line of identity, 4 PM values equal 4 AM values.

cantly correlated ($r = 0.63$, $P = .009$), and there were no significant differences in mean values at these 2 times ($P = .94$). Six of the 16 children had PC₂₀ values that were greater than 2-fold different between the 4 PM and 4 AM measurements (Fig 1, B). Three of these were more reactive (requiring less methacholine) at 4 PM, and 3 were more reactive at 4 AM.

For the 11 subjects studied a second time (data not shown), the mean values of PC₂₀ at 4 PM (0.95) and at 4 AM (1.82) were correlated ($r = 0.70$, $P = .02$). These values were correlated with those measured at comparable times during the first study (4 PM: $r = 0.60$, $P = .05$; 4 AM: $r = 0.55$, $P = .08$). However, at the second study, the 4 AM values were significantly higher than the 4 PM values ($P = .04$). Of the 11 subjects, 5 had PC₂₀ values that were greater than 2-fold different between 4 PM and 4 AM. All 5 were more reactive at 4 PM (requiring less methacholine at that time). Only 2 of these subjects also had diurnal variability in PC₂₀ on the first day of the study; both of these subjects exhibited more reactivity at 4 AM than at 4 PM on the first day of the study. However, the overall

effect of diurnal variability in PC₂₀ was 1.27 and non-significant (Table II).

Diurnal variability in HVD

Mean values at 4 PM (0.017 V_e/6 sec/saturation) and at 4 AM (0.014 V_e/6 sec/saturation) were not correlated ($r = 0.008$, $P = .98$), but there was no significant difference between values at these 2 times ($P = .47$). Six subjects exhibited an increase in HVD, 9 showed a decrease, and 1 showed no change from 4 PM to 4 AM (Fig 1, C). Values obtained during the second study (mean values at both 4 PM and 4 AM = 0.013) were similar to those of the first study day, but there was no correlation across days of study for values measured either at 4 PM or 4 AM. There was no effect of diurnal variability by using data from both days of study (Table II).

Diurnal variability in vagal tone

Holter recordings were analyzable for 13 of the 16 subjects. Mean values for vagal tone at 4 PM (6.3 V) and at 4 AM (7.2 V) were not correlated ($r = -0.02$, $P = .96$),

and the difference between them was significant ($P = .05$). Eight subjects exhibited higher vagal tone, and 5 subjects exhibited lower vagal tone at 4 AM as compared with 4 PM values (Fig 1, D). At the second study, mean values for vagal tone were slightly higher at 4 PM (6.4 V) than at 4 AM (6.0 V) but not significantly different ($P = .25$). There were marginally significant correlations between vagal tone measured at 4 PM across the 2 days of study ($r = 0.70$, $P = .07$), but vagal tone was not correlated for the 4 AM values ($r = -0.20$, $P = .67$). There was no overall effect of diurnal variability in vagal tone as determined with data from both days of study (Table II).

Correlations among measures

Correlations among measures on day 1 of the study were computed. At 4 PM, mean values for PC₂₀ and FEV₁ were correlated ($r = 0.54$, $P = .03$). The correlations between mean values of HVD and vagal tone were marginally significant ($r = -0.63$, $P = .07$). None of the other correlations were significant. At 4 AM, values of PC₂₀ were correlated with those of FEV₁ ($r = 0.78$, $P = .0003$) and HVD ($r = 0.58$, $P = .03$). The correlations between FEV₁ and HVD values were marginally significant ($r = 0.48$, $P = .09$). None of the other correlations reached significance.

The change in each measure from 4 PM to 4 AM was then compared across the different measures, and correlations were computed. There were strong positive correlations between the change in PC₂₀ reactivity and the change in both FEV₁ ($r = 0.79$, $P = .0003$) and HVD ($r = 0.66$, $P = .01$). Furthermore, there was a significant correlation between the changes in FEV₁ and HVD reactivity ($r = 0.54$, $P = .05$). The relationship between changes in PC₂₀ reactivity and vagal tone was negative and marginally significant ($r = -0.49$, $P = .09$).

Diurnal variability and subject characteristics on the first day of study

To determine whether the magnitude or direction of differences in values as a function of time of day were related to subject characteristics, correlations and *t* tests were computed with respect to the change in values from 4 PM to 4 AM for each dependent variable. There was a trend for subjects who were older ($r = 0.56$, $P = .06$) or who had more severe disease ($r = 0.5$, $P = .10$) to show a greater increase in vagal tone from 4 PM to 4 AM. There was a significant relationship between age and the direction of change in vagal tone; subjects with an increase in vagal tone from 4 PM to 4 AM were older (13.9 ± 1.9 years) than those with a decrease (11.5 ± 2.3 years) ($P = .04$). Age accounted for 27% of the variance in the diurnal variability of vagal tone. There were no significant correlations between demographics (including Tanner scores), clinical characteristics, or current medications and any other measures of diurnal variability.

DISCUSSION

Pulmonary function (FEV₁) and airway reactivity to methacholine (PC₂₀) measured at 4 PM and 4 AM in 16

adolescent children with a broad range of asthma severity were highly correlated within the individuals studied. However, no systematic differences occurred in FEV₁ or PC₂₀ between 4 PM and 4 AM. Although there was a broad range of pulmonary function and airway reactivity by asthma severity, the variability was a characteristic of the individuals and not influenced by the time of study.

The original intent of this study was to identify diurnal variability of airway reactivity in adolescents with asthma by using a 2-fold difference in PC₂₀ values obtained at 4 PM and 4 AM as a criterion. We observed no systematic differences in PC₂₀, despite having a power of .80 to detect such differences. Although 39% of the children had greater than 2-fold differences between the PC₂₀ values obtained at 4 PM and 4 AM, half of these had more reactivity at 4 PM. This contrasts with the data from adults in whom diurnal variability was consistently a result of more reactivity at 4 AM. In this study diurnal variability was not related to age, sexual maturation, sex, race, asthma severity, or history of prominent nocturnal wheeze. Thus the hypothesis that diurnal variability in airway reactivity would correlate with maturation was not supported. In addition, the hypotheses that increased airway reactivity would reflect an increase in vagal tone and a decrease in HVD were not supported.

The observed stability of FEV₁ and PC₂₀ between the afternoons and nights differs from that reported previously. For example, Martin et al^{9,24} have demonstrated decreases in FEV₁ and increased sensitivity to methacholine when studied at 4 AM compared with 4 PM. Changes in airway reactivity were more prominent in those patients who had marked decrements in FEV₁ but occurred in individuals with stable pulmonary function as well. There are several possibilities for the differences between the results in these studies and our findings. All other studies of nocturnal asthma and diurnal variability of airway obstruction and reactivity have been performed with adults. In addition, other reports have included subjects who may have had unstable asthma, with a certain percentage of subjects having reactivity to the normal saline diluent, particularly when studied at 4 AM. This characteristic would have disqualified subjects from our study. Thus the differences could be related to the age of the subjects or the stability of the asthma at the time of the study. Other asthmatic children, particularly those with more severe disease or more predominance of nighttime symptoms, might have variability even with the same degree of clinical stability. The degree of airway reactivity is known to vary with time, increasing with stimuli that increase airway inflammation and decreasing with corticosteroid therapy.²⁵ Patients with more severe disease tend to have more reactivity to methacholine. It is certainly possible that the degree of diurnal variability in airway reactivity would vary with clinical severity of illness as well.

Similar to the findings with airway reactivity, values for HVD measured at 4 AM were not different than those at 4 PM. These data suggest that, as with airway reactivity, there is not a sleep-associated abnormality in HVD inherent in

adolescent subjects with asthma. The results did not differ when the adolescents in the rapid phase of maturation (Tanner levels 2 to 4) were examined separately.

There were significant correlations across measures used to assess airway obstruction, reactivity, and responsiveness to hypoxemia. These correlations were strongest between pulmonary function and airway reactivity, a finding of other studies.⁹ Correlations were also observed for the 4 AM studies between HVD and the measures of airway function. Vagal tone showed the expected negative correlation with HVD, but the correlation was significant only at 4 PM. Vagal tone was not correlated with airway reactivity, suggesting that vagal tone in the airways may not be tightly correlated with systemic tone.

Taken together, the data on airway reactivity, HVD, and the other measures modulated by cholinergic neural mechanisms do not identify any systematic diurnal variation that would place an adolescent at risk for nighttime problems with asthma. It is possible that such diurnal variations could become prominent at times of clinical instability not present at the time of study of these adolescents.

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