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Children with Nocturnal Asthma Wheeze Intermittently During Sleep

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Nocturnal asthma indicates poor overall control of asthma and adversely affects the quality of life of the patient. The purpose of the present study was to compare the objective measurement of nocturnal wheeze with clinical state, recall of symptoms, and changes in lung function. Nine asthmatic children aged 9 to 16 years were followed with an asthma diary and diurnal measurement of peak flow for a week before the nocturnal study; all but two were apparently well controlled. Breath sounds were recorded and analyzed continuously overnight to quantify wheeze using a phonopneumography sensor attached over the trachea. The analytical system (PulmoTrack) utilized an algorithm to detect wheeze and reject interference. The wheeze rate (Tw/Ttot = duration of wheeze/duration of recording) was calculated minute by minute throughout the night. Recordings lasted over 8 hours and all but two children had wheeze lasting for a total time of between 11 and 87 minutes. The pattern of wheezing was very variable during sleep, with episodes of wheeze separated by periods of quiet breathing. There was no relationship between subjective perception of nocturnal asthma, forced expiratory volume in 1 s (FEV_1) next morning, and the objective measurement of wheeze. Total overnight wheeze was significantly related to the total diary symptom score and to the (small) diurnal variability of peak expiratory flow (PEF). Four of the seven children with asthma who were apparently well controlled had considerable amounts of wheeze during the night that was episodic in nature and unrelated to conventional measures of lung function or nocturnal symptoms.

Keywords acoustic respiratory monitoring; asthma control; childhood asthma; nocturnal asthma; phonopneumography

Introduction

It is common experience that many asthmatics feel worse at night. Indeed over 300 years ago, Sir John Floyer noted, "At first waking, about one or two of the Clock in the Night, the Fit of the Asthma more evidently begins—" (1). Nocturnal worsening of asthma may be accompanied by reduced lung function on waking, for which Prof. Turner-Warwick coined the termed "morning dipping" (2) and some early studies appeared to indicate that the severity of morning dipping reflected the severity of asthma (3, 4). The reporting of nocturnal exacerbations of asthma forms one of the important criteria for defining asthma severity and the level of control according to all the various published guidelines for the management of asthma, including the most recent Global Initiative for Asthma (GINA) guidelines (5). This of course presupposes that reporting by the patient is reliable and that they neither overestimate the incidence of nocturnal asthma nor sleep through an attack. From the few objective studies available, it is likely that nocturnal asthma is almost certainly unrecognized by many patients, and even those with marked "morning dipping" often fail to report nocturnal asthma (6–8).

In a previous study from our group using the noninvasive recording of breath sounds and detection of wheeze (9), we found that 7 out of 12 young patients reported nocturnal asthma symptoms but objective wheezing was only present in 2 of them and 1 other patient with sustained nocturnal wheezing did not report any wheeze the next morning. In that study, the acoustic definition of wheeze used by the computer algorithm was limited to the frequency range of 150 to 800 Hz and monophonic inspiratory wheeze was not included. The upper limit of sensitivity for a modern clinical stethoscope is about 1000 Hz (10) and it is possible that the extent of nocturnal wheeze was underestimated. Modern phonopneumography (PPG) acoustic sensors have a frequency range that extends to about 4000 Hz (11) and such sensors are therefore able to detect high-frequency wheezing that would not be audible with a clinical stethoscope. Moreover, in a study of the acoustic nature of wheeze in children during bronchial challenge, we have shown that in 29% of positive challenges, the onset of a positive response was detected by wheeze that was both inspiratory and monophonic (12); this type of wheeze should be included in the objective quantification of wheeze.

The present descriptive study of nocturnal asthma was undertaken in children resident in an institution for asthmatic children in the Italian Alps. Equipment and computer algorithms able to continuously detect wheeze over a wide frequency span was used in order to explore the pattern of nocturnal asthma during natural sleep and its relationship to clinical status and subjective complaints.

Methods

Patients

Studies were undertaken in nine unselected young asthmatic patients (all male), aged 9 to 16 years (mean 13.9 ± 2.2 [*SD*] years), resident in an institute for asthmatic children in the Italian Alps. The only inclusion criteria were a

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confirmed diagnosis of asthma, no other relevant medical conditions, and willingness to participate in the study. No attempt was made to include children with asthma of different severities and no normal children were studied. Informed consent to participate in the study was obtained from the parents or legal guardians of the children and the institutional ethics committee of the University of Verona approved the study.

Symptom Recording and Nocturnal Study

For 1 week before the nocturnal study, each child kept an asthma diary in which night time and daytime symptoms, and limitation of activity, were scored on a scale of 0 to 3, giving a maximum weekly score for each symptom of 21 and a maximum total diary score of 63. Each evening and morning before taking medication peak expiratory flow (PEF) was measured with a Wright peak flow meter (Clement Clarke International, Harlow, England) as the best of three efforts. On the evening before the nocturnal study and on waking the next morning, lung function was measured by spirometry (Vitalograph Compact, Buckingham, England). For the nocturnal study, a PPG sensor was attached over the trachea and connected to a data storage and analysis module (PulmoTrack 1010; Karmel Medical Acoustic Technologies, Yokneam Illit, Israel). An updated version of the computer software (KarmelSonix, Haifa, Israel) was used to analyze the results. Recording ran continuously from bedtime until waking next morning when the child was asked to score any overnight symptoms on a scale of 0 to 3.

Data Analysis

The mean of individual items and the total score from the weekly diary were calculated and the diurnal variation of peak flow was calculated as the amplitude % mean ((morning − evening)/(morning + evening) × 50)) averaged over the week of diary keeping, whereas that for forced expiratory volume in 1 s (FEV_1) was calculated from the nocturnal study day.

The wheeze rate (Tw/Ttot) was calculated continuously minute by minute from the overnight recording as the duration of wheeze/duration of recording × 100. The program accepted wheeze as musical monophonic or polyphonic sounds with a duration of at least 100 ms, in accordance with the European Task Force report on computerized breath sounds (13–15). Wheezing that would not normally be audible with a regular stethoscope was excluded by accepting only wheeze with a frequency below 1200 Hz. Acoustic events having a cumulative duration of less than 3 s in any one minute (Tw/Ttot < 5%) were assumed unlikely to be clinically relevant and were excluded from the calculation of wheeze rate. The record was also checked manually to ensure that artefacts such as snoring had been excluded. The nocturnal wheeze was quantified by calculating three indices:

- Tot-TWz = the number of minutes for which Tw/Ttot was ≥ 5%
- TWz-max = the longest period for which Tw/Ttot was = 5% continuously
- nWz-5 = the number of episodes for which Tw/Ttot was ≥5% for at least 5 consecutive minutes

Statistical Analyses

Data that were normally distributed were expressed as the mean and standard deviation and the relationships between variables were explored by regression analysis.

Results

Relevant clinical details and FEV_1 and PEF data for the children are summarized in Table 1. Four of the children were receiving as-needed bronchodilator medication alone, one was receiving a leukotriene inhibitor, and the other four children were receiving inhaled corticosteroids as preventative medication. Of the nine patients, five were effectively asymptomatic for the week before the study, with a total diary score of 3 or less (out of a maximum of 63). One child scored 5 (TM) and the remaining three children (PF, PM, BR) had diary scores between 14 and 23 and all three were receiving inhaled corticosteroids on a regular basis. Three children had low evening and morning FEV_1 values (≤55% predicted) and two of them (PM, BR) reported nocturnal symptoms. One of them (BR) had a large morning dip of FEV_1 but this may have been exaggerated due to poor effort because his diurnal variation of PEF was only 2.7%. Based on the most recent Global Initiative for Asthma (GINA) guidelines (5), all but two of the children would be classified as well controlled using the information from their weekly diary and the results of spirometry. Two children, PM and BR (Table 1), would be classified as uncontrolled.

The mean duration of nocturnal recording was 8.2 ± 0.7 (range 6.3–8.7) hours and the results of the measurement of nocturnal wheeze compared with other parameters are summarized in Table 2. In two children (MF, MM), there was

Table 1.—Clinical details.

Child	Rx#	Weekly diary score	Weekly amplitude % mean PEF (%)	Evening FEV_1 (%)	Morning FEV_1 (%)	Amplitude % mean FEV_1 (%)	Nocturnal symptoms	GINA* control
TD	2	3	0.6	102	99	1.5	0.0	C
PF	3	14	4.4	80	76	4.1	0.0	C
BF	3	3	4.1	62	52	8.8	0.0	C
PM	3	23	5.8	63	55	6.8	3.0	U
BR	3	17	2.7	62	32	31.9	3.0	U
BN	1	0	0.6	93	101	−4.1	0.0	C
TM	1	5	2.5	91	97	−3.2	0.0	C
MF	1	0	−1.1	94	106	−3.2	0.0	C
MM	1	0	0.6	75	98	−13.3	0.0	C

#Rx, regular medication; 1 = bronchodilators as needed only; 2 = leukotriene inhibitor; 3 = inhaled corticosteroids.
*GINA control = classification of adequacy of control of asthma using the most recent GINA guidelines (5).

TABLE 2.—Nocturnal wheeze, symptoms, and morning FEV_1.

Child	Tot-TWz (min)*	TWz-max (min)†	nWz-5‡	Weekly diary score	Nocturnal symptoms	Low morning FEV_1
TD	15	4	0	3	No	No
PF	66	30	2	14	No	No
BF	39	8	2	3	No	Yes
PM	87	11	6	23	Yes	Yes
BR	20	5	1	17	Yes	Yes
BN	20	8	2	0	No	No
TM	11	3	0	5	No	No
MF	0	0	0	5	No	No
MM	0	0	0	0	No	No

*Tot-TWz (min) = total number of minutes during the night with a wheeze rate (Tw/Ttot) greater than 5%.
†TWz-max (min) = longest single period with Tw/Ttot continuously >5%.
‡nWz-5 = number of episodes with Tw/Ttot > 5% lasting at least 5 min continuously.

no objective evidence of wheeze and both had no nocturnal symptoms and a normal FEV_1 (>97% predicted) next morning. The whole nocturnal record for one of these children (MF) is shown in Figure 1. Four children had a modest amount of nocturnal wheeze lasting between 11 and 20 min in total and three of them had no nocturnal symptoms and a normal FEV_1 next morning. Three children (PF, BF, PM) had considerable overnight wheeze, with a total duration of 39 to 87 min and the longest continuous episode lasting 8 to 30 min. Only one of these three children (PM) complained of overnight symptoms and had a low FEV_1 (55%) the next morning, one (BF) had a low FEV_1 (52%) but no symptoms, and the third (PF) had a good FEV_1 (76%) and no symptoms.

The continuous record of overnight wheeze from the child (PM) with the longest total amount of wheeze is shown in Figure 2. As can be seen, this child had multiple episodes of wheeze greater than 5% of varying severity during the night, which occurred in three separate clusters with relatively long wheeze-free periods in between lasting 1.5 to 2.0 h. This child had a low FEV_1 on the evening before the study (63%) and on the next morning (55%) and also complained of overnight symptoms but did not request any additional medication during the night. He had a high weekly symptom score from the diary record (23 out of a maximum of 63), which included symptoms, mostly mild, on 6 of the 7 nights. He was being treated with inhaled corticosteroids and long-acting bronchodilators on a regular basis. However, another child (PF) also had considerable nocturnal wheeze, with one long episode lasting about 30 min beginning just over half an hour after midnight and several shorter episodes during the night and early morning (Figure 3), but this child reported no nocturnal symptoms and his FEV_1 the next morning was 76% of predicted. This child was receiving regular inhaled corticosteroid and a short-acting bronchodilator as needed. His total weekly diary score was 14. Of the two children with uncontrolled asthma by the GINA classification (PM and BR), one had the most severe nocturnal wheeze (87 min) but the other only had a moderate amount (20 min) of wheeze. However, all the other children with wheeze, including the two with 39 and 66 min of wheeze, respectively, would have been classified by GINA as controlled.

The relationship between the total amount of nocturnal wheeze >5% and the total weekly diary scores for the nine children are shown in Figure 4. The correlation between nocturnal wheeze and diary score was significant ($r^2 = .62$, $p = .01$), as was the correlation of nocturnal wheeze with amplitude % mean PEF ($r^2 = .79$, $p = .001$), but the amplitude % mean PEF was very low and never reached above 5.8%. Although two of the three children with the most nocturnal wheeze had low FEV_1 values the next morning, one did not, and the correlation between nocturnal wheeze, morning

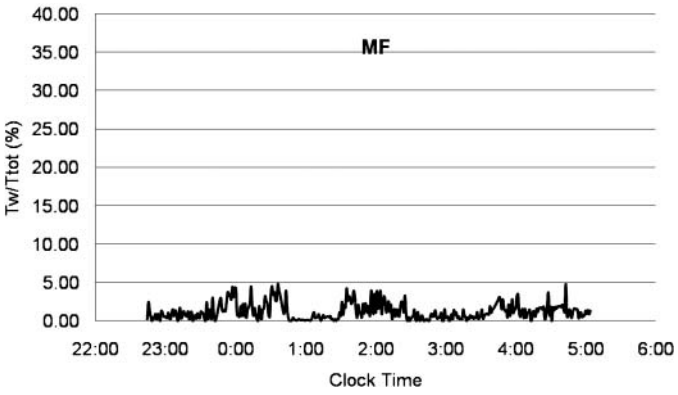

FIGURE 1.—Continuous overnight record of wheeze rate (Tw/Ttot) from the child (MF) with no wheeze >5%, no symptoms and a normal FEV_1 next morning.

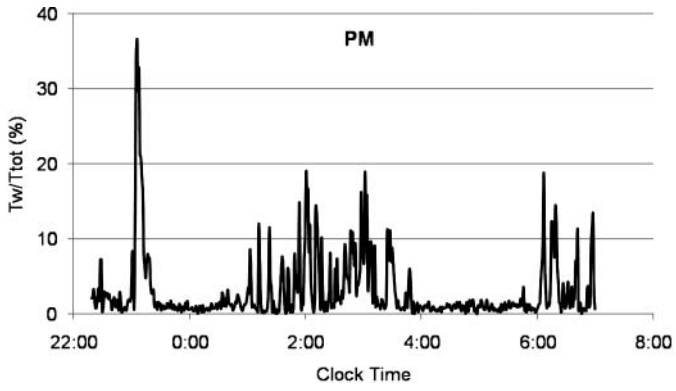

FIGURE 2.—Continuous overnight record of wheeze rate (Tw/Ttot) from the child (PM) with the most severe nocturnal asthma who complained of symptoms and had a low FEV_1 next morning.

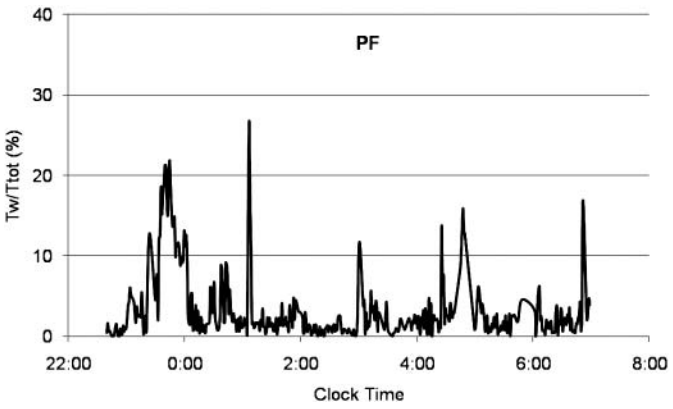

FIGURE 3.—Continuous overnight record of wheeze rate (Tw/Ttot) from the child with the next most severe nocturnal asthma (PF) who had no symptoms and had a normal FEV_1 next morning.

FEV_1, and all other clinical or physiological measures were not significant.

DISCUSSION

This study has shown that nocturnal wheeze in children with asthma is often episodic during the night, with attacks being separated by wheeze-free periods. Although the child with the most severe nocturnal wheeze was almost certainly poorly controlled judged by his diary scores and lung function, another child with very significant nocturnal wheeze was completely unaware of any problem at night and had a normal FEV_1 the next morning. Although the total duration of nocturnal wheeze was correlated with the week-long diary scores, the severity of the nocturnal wheeze was unrelated to the report of nocturnal symptoms by the children. Although wheeze can occur in conditions other than asthma in the presence of airways obstruction, in the present study where all the children had clinical asthma and no other pulmonary problems, it seems reasonable to conclude that in several of them with nocturnal wheeze but no symptoms, the severity of nocturnal asthma was underestimated.

In this study we were able to record and automatically analyze the breath sounds continuously in a fashion that has not previously been possible due to advances in the software now available. Although we restricted wheeze to frequencies below 1200 Hz to approximate the range of sounds heard through a regular stethoscope, in fact we recorded up to a frequency of 4000 Hz and detected a small amount of additional high frequency wheeze that would not have been audible with a regular stethoscope (although probably would have been audible with the naked ear). In fact in the seven children with nocturnal wheeze, the wheeze below 1200 Hz accounted for an average of 85% ± 17% of the total wheeze so that there was about 15% of additional high-frequency wheeze.

In a previous study (9), we noted that of 16 rather older adolescents with apparently poorly controlled asthma, nocturnal wheeze was only detected in 3, of whom only 1 reported nocturnal symptoms, whereas of 7 who reported symptoms, no objective wheezing was recorded in 5. All three subjects with objective nocturnal wheezing had low FEV_1 values (≤60% predicted) the next morning. The results of the present study showed a broadly similar pattern, with most of the children with objective wheeze having no symptoms and with two of the three with the most severe nocturnal wheeze having a low FEV_1 the next morning. The children in the present study do not appear to have more severe asthma than those in the previous study but we detected more wheezing during the night. This may partly be explained by the fact that the previous study only included wheeze with a frequency below 800 Hz. Examining the data from the present study we found that a cut-off below 800 Hz substantially reduced the wheeze in two children (to 20% and 29%, respectively, of the total wheeze with a cut-off <1200 Hz) and moderately reduced it in one other (to 64%).

Apart from our previous study using acoustic monitoring (10), there have been very few published studies in which asthmatic patients have been observed and monitored continuously during the night. These studies mostly used invasive technology such as the measurement of pulmonary resistance using an oesophageal balloon and face mask containing a pneumotachygraph in small numbers of patients selected specifically because of symptomatic complaints of nocturnal exacerbations of asthma (6, 7, 16, 17). All four studies showed that the asthmatics developed an increase in resistance during the night, but some of the patients in the two studies for which this information is provided failed to wake (6, 7). Lenclud et al. (17) measured wheeze during the night with a tracheal sound analyzer in addition to the measurement of pulmonary resistance. It is interesting to see from the data on two patients in the illustration provided in their paper that they also demonstrated clusters of wheeze during the night, similar to the pattern we found in the present study.

Because we did not measure lung function during the night, we only have the acoustic data as an indication of airway patency during the night. Previous clinical studies of the relationship between audible wheezing and lung function suggest that wheezing is heard when the FEV_1 (or PEF) falls to approximately 50% to 60% of predicted (18–21). Other studies in which auscultation to detect wheeze and lung function was measured during bronchial challenges also suggest that FEV_1 has to fall considerably before wheeze appears (22–25). In all of these bronchial challenges, the baseline FEV_1 beforehand was close to normal and the implication is that FEV_1

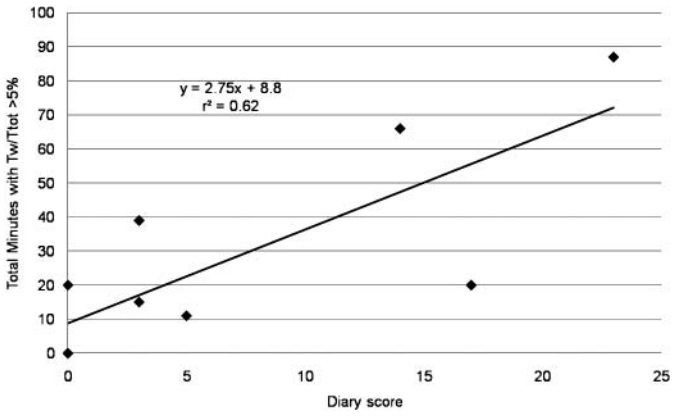

FIGURE 4.—Total number of minutes during the night with Tw/Ttot > 5% related to the total diary symptom score recorded over 1 week.

has to fall to about 65% to 70% of predicted before wheeze appears. Hyperinflation is also a common problem in asthma but its effect on nocturnal asthma has not been studied to the best of our knowledge.

In conclusion, we have shown that children with asthma have considerable amounts of wheeze during the night that is episodic in nature and poorly related to conventional measures of lung function, subjective symptoms, or current estimates of control.

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Declaration of Interest

Prof. S. Godfrey receives a consultation fee and holds stock option in KarmelSonix, Prof. N.Gavrieli is the CMO and shareholder of Karmelsonix, and Mrs. Diana Goldstein is a part time student technician and employee of Karmelsonix. Dr C. Irving was a former employee of KarmelMedical and no longer has any association with KarmelSonix. None of the other authors have any financial relationship with KarmelSonix.

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