Passive Nocturnal Physiologic Monitoring Enables Early Detection of Exacerbations in Children with Asthma

A Proof-of-Concept Study

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Abstract

Rationale: Asthma management depends on prompt identification of symptoms, which challenges both patients and providers. In asthma, a misapprehension of health between exacerbations can compromise compliance. Thus, there is a need for a tool that permits objective longitudinal monitoring without increasing the burden of patient compliance.

Objectives: We sought to determine whether changes in nocturnal physiology are associated with asthma symptoms in pediatric patients.

Methods: Using a contactless bed sensor, nocturnal heart rate (HR), respiratory rate, relative stroke volume, and movement in children with asthma 5–18 years of age ($n = 16$) were recorded. Asthma symptoms and asthma control test (ACT) score were reported every 2 weeks. Random forest model was used to identify physiologic parameters associated with asthma symptoms. Elastic net regression was used to identify variables associated with ACT score.

Measurements and Main Results: The model on the full cohort performed with sensitivity of 47.2%, specificity of 96.3%, and accuracy of 87.4%; HR and respiratory parameters were the most important variables in this model. The model predicted asthma symptoms 35% of the time on the day before perception of symptoms, and 100% of the time for a select subject for which the model performed with greater sensitivity. Multivariable and bivariable analyses demonstrated significant association between HR and respiratory rate parameters and ACT score.

Conclusions: Nocturnal physiologic changes correlate with asthma symptoms, supporting the notion that nocturnal physiologic monitoring represents an objective diagnostic tool capable of longitudinally assessing disease control and predicting asthma exacerbations in children with asthma at home.

Keywords: asthma; pediatric asthma; longitudinal monitoring; asthma control

Asthma is one of the most common chronic diseases in children, affecting as many as 8.5% of children in the United States, with even higher rates among African Americans

and inner city and urban youth (1, 2). The clinical course is difficult to predict. Most patients presenting with an acute asthma exacerbation are not on controller

medications (3). Asthma also remains particularly challenging to manage, and is poorly controlled in the majority of subjects with asthma (3, 4). These challenges are

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At a Glance Commentary

Scientific Knowledge on the

Subject: Currently, there are no diagnostic tools that can sensitively and objectively detect the onset of an asthma exacerbation. Although peak expiratory flow may decrease as long as 2 weeks before an asthma exacerbation, the utility of the measure is compromised by variability, uncertain compliance, and being effort-dependent. Whether changes in physiologic parameters, such as heart rate or respiratory rate, occur before the development of clinically evident asthma symptoms remains unknown.

What This Study Adds to the

Field: This study provides data supporting the notion that physiologic parameters, such as heart or respiratory rate, can be used to detect the onset of an asthma exacerbation before clinically apparent asthma symptoms. Moreover, the data represent proof of concept that passive physiologic monitoring can be used in the home environment of children with asthma to both longitudinally monitor asthma control and provide a sensitive indicator of an impending asthma exacerbation.

highlighted by the absence of diagnostic tools that can reliably predict a disease exacerbation, such that the best tool for predicting asthma exacerbation remains history of prior exacerbation (5).

The absence of a reliable, reproducible diagnostic tool capable of predicting asthma exacerbations or assessing disease control compromises the care of children with asthma. Although multiple factors underlie the ongoing use of less-than-optimal tools to assess asthma control, most tools are compromised by a reliance on subjective information to determine the degree of control. Multiple studies support the proposition that patients, parents, and clinicians generally overestimate how well asthma is controlled (6, 7). Use of medication, visits to health care providers, and even avoidance of triggers are all contingent upon caregiver and patient perception of control. Furthermore, the perception of both caregivers and children

Table 1. Characteristics of the 16 Patients Included

Subject Demographics	
Subjects, <i>n</i>	16
Age at enrollment, yr	5–17 (average = 9.75)
Sex, F/M, <i>n</i>	3/13
Asthma severity, <i>n</i>	
Intermittent	2
Mild persistent	4
Moderate persistent	9
Severe persistent	1
Uses controller medication, <i>n</i>	
ICS	15
ICS + LABA	4
LTRA	3
Omalizumab	2
Use of oral steroids in preceding year, <i>n</i>	
At least once	11
Four or more times	4
Emergency department visit or hospitalization for asthma in preceding year, <i>n</i>	
Visited emergency department	11
Hospitalized	7
Atopy, <i>n</i>	
Atopic	14
Perennial/seasonal/mold	8/8/3

Definition of abbreviations: ICS = inhaled corticosteroid; LABA = long-acting β agonist; LTRA = leukotriene receptor antagonist.

may be confounded by physiologic differences in presentation, and financial or personal conflicts, such as the need to attend school, go to work, have a pet in the home, or attend social gatherings (8–11). The inadequacy of current diagnostic tools is further illustrated by the episodic

exacerbations that occur even after long time intervals of apparent control (12–14).

These observations prompt the question of whether tools currently available to manage asthma and assess the efficacy of management are sufficiently sensitive. Current strategies to assess control include

Table 2. Data Available for Analysis for Each Subject

Subject ID	Nights of Recorded Data	Nights with Asthma Symptoms/Total Nights with Information on Asthma Status	Nights with Asthma Symptoms/Nights with Information on Asthma Status and Nightly Physiologic Data Complete and Reliable
1	210	22/72	16/50
2	68	2/33	2/27
3	214	38/105	35/90
4	28	0/28	0/28
5	92	0/81	0/76
6	53	0/53	0/38
7	17	0/17	0/12
8	191	4/162	4/107
9	9	0/9	0/9
10	177	22/136	21/124
11	81	0/66	0/57
12	166	44/78	44/77
13	115	8/87	7/57
14	125	14/52	12/32
15	118	1/73	1/70
16	166	27/61	19/37

Table 3. Performance of Random Forest Model on Nightly Data in Detecting Asthma Symptoms

	Model Symptom Prediction		
	No	Yes	Total
Subject reported symptoms			
No	703	27	730
Yes	85	76	161
Total	788	103	891

Sensitivity = $76/161 = 47.2\%$; specificity = $703/730 = 96.3\%$; accuracy = $(703 + 76)/891 = 87.4\%$.

measurement of peak expiratory flow in the home. This parameter is notable for being effort dependent and highly variable, even in the same subject, thereby meaningfully limiting its utility. Assessment of pulmonary function in the clinic provides information at only a single point in time and is also, generally, highly effort dependent. Moreover, proper assessment of control needs to occur not simply during a single clinic visit, but over the longer term, in the context of the home environment. Tools

used to assess disease management include validated asthma control questionnaires, which are frequently employed in clinical trials (15). Although surveys can be administered remotely and endeavor to reflect asthma control over an extended time interval, the efficacy of surveys is compromised by need for patients and families to recall signs and symptoms from the prior 7–28 days and to accurately perceive and report disease symptoms (15–17).

Although there is consensus surrounding the importance of longitudinal and objective assessment of asthma control in the home environment, there are surprisingly few well-accepted tools that objectively assess asthma control in the home environment. A parameter that has shown promise in this arena is changes in peak expiratory flow that can occur up to 2 weeks before an exacerbation (18). The rate of nocturnal cough has also been associated with asthma control and severity of exacerbation (19). Whether physiologic parameters might be used to assess asthma control and be an early warning sign of disease exacerbation remains unknown.

The present prospective observational study was undertaken to test the hypothesis that, in children with asthma, nocturnal

heart rate (HR), measured by passive nocturnal physiologic monitoring, reflects disease control and represents a sensitive sign to diagnose asthma exacerbation. To test this hypothesis, ballistocardiography (BCG) was used. It is a technique that can measure HR, HR variability (HRV), calculated respiratory rate (RR), and relative stroke volume (SV; integral of the detected acceleration pulse from the BCG) by recording the vibrations generated by blood pumped into the great vessels with each cardiac cycle. The results from BCG monitoring were compared with a widely accepted self-reporting metric, asthma control test (ACT), and clinically validated against spirometry and specialist assessment. Some of the data shown here have been previously reported in the form of an abstract (20).

Methods

Study Population

We performed a prospective observational study of nocturnal physiologic monitoring of pediatric patients with asthma from 2016 to 2017. Families of patients with a diagnosis of asthma were approached in either the outpatient arena or at the conclusion of a hospitalization at Lucille Packard Children's Hospital (Stanford, CA). After procuring informed consent, patients were enrolled and subjects' parents completed a baseline questionnaire regarding asthma severity, asthma control, comorbidities, medications, and home environment. Recruitment occurred from August 2016 to April 2017.

To be included in the analytic cohort, patients had to meet the following inclusion criteria: age 5–18 years with a diagnosis of persistent asthma; sleeping in a bed alone; internet availability; and willingly and cognitively able to sign informed consent and/or provide assent. Patients with fewer than two time points of survey data were excluded. Patients with preexisting neurological, cardiopulmonary, psychiatric, or sleep-disordered breathing diagnoses were excluded.

The protocol was approved by the Institutional Review Board of Stanford University and the parents of all participants provided written informed consent. The study was supported by a Spectrum Stanford Clinical and Translational Science Award, the program of which is led by the National

Figure 1. Top device output variables according to mean decrease in accuracy (MDA) from random forest algorithm. The MDA is the decrease in accuracy of model predictions when a variable is removed from the model by permuting its values so the values are unrelated to the outcome. Omitting the information from a variable that is not important would not change the model accuracy, and the MDA would be 0. Omitting the information from a variable important to the model would decrease the model's accuracy substantially, and the MDA would be relatively greater than 0. Statistical measures of heart rate were the top five most important variables for prediction of loss of asthma control. HR = heart rate.

Table 4. Performance of Random Forest Model on Nightly Data in Detecting Asthma Symptoms for Subject 3

	Model Symptom Prediction		
	No	Yes	Total
Subject reported symptoms			
No	50	5	55
Yes	8	27	35
Total	58	32	90

Sensitivity = $27/35 = 77.1\%$; specificity = $50/55 = 90.9\%$; accuracy = $77/90 = 85.5\%$.

Center for Advancing Translational Sciences at the NIH. The study was designed by investigators at Stanford University Medical Center and Lucille Packard Children's Hospital. The study monitoring and statistical analysis were performed at Stanford University (Institutional Review Board Protocol 34541). Raw data from the physiologic monitors were processed by Tueo Health.

Study Device

A commercially available BCG accelerometer-based passive bed sensor (SCA11H; Murata Technologies) was used for data collection. A home visit was performed wherein the SCA11H device was placed on the subject's mattress, secured under the bed sheet. The device was attached to the mattress using an elastic strap and did not directly contact the subject. The device was configured to communicate with the participant's home WiFi. The device measured HR, calculated

Table 5. Performance of Random Forest Model on Nightly Data in Detecting Asthma Symptoms for Subject 10

	Model Symptom Prediction		
	No	Yes	Total
Subject reported symptoms			
No	97	6	103
Yes	13	8	21
Total	110	14	124

Sensitivity = $8/21 = 38.1\%$; specificity = $97/103 = 94.2\%$; accuracy = $105/124 = 84.7\%$.

RR, and relative SV (integral of the detected acceleration pulse from the BCG) using a microprocessor within the device. Prior work in a sleep laboratory compared the output of the device to polysomnography, which included electrocardiography measure for HR and thorax and abdomen belts for respiratory effort. There was not a significant difference in HR, HRV, or RR between the SCA11H device output and the polysomnography results. HR had the strongest correlation ($r = 0.97$) (21). This sensor is also able to detect large-scale movements, such as the child rolling or moving in bed. There were no instances of device failure. Failure of data collection was most often due to changes in subjects' WiFi password or the device inadvertently being unplugged. Absence of data was otherwise most often due to the sensor being dislodged from the bed or the subject not sleeping in bed.

Outcome Measures

Every 2 weeks, data were collected from parents of subjects on changes in asthma control (using ACT, childhood ACT, and reporting of symptoms) or medications. Subjects did not maintain a symptom diary. Specific dates of symptom onset and resolution were ascertained from subject recall. The ACT score was not modified, and was collected every 2 weeks to more accurately assess for relationship between score and physiologic change.

The primary outcome was the time period during which onset of asthma symptoms occurred. A symptomatic period was defined as the time between the date of asthma onset and the date of asthma resolution, as reported by the subjects' parents. The time interval 14 days before date of symptom onset and 14 days after date of resolution were excluded from the main analysis to avoid erroneously considering days in which subjects had signs of asthma, but did not perceive symptoms, as the literature indicates that there are often discrepancies between subject perception and actual worsening of asthma (7, 11). Time periods during which asthma symptom status was indeterminate, such as when asthma symptoms were reported, but date of onset was missing, were also set as having missing outcome.

Device Output Variables

In this analysis, the following device output variables were included: HR; RR; HRV;

calculated RR variability (RRV); SV; HR percentile based on age; RR percentile based on age; movement; relative $\dot{Q}$ ($\dot{Q} = SV \times HR$); and $\dot{V}O_2$ (proxy for $\dot{V}O_2 = SV \times RR$). Percentile based on age was derived from published data (22). For each of these device output variables, the following statistical measures were computed: count of measurements per night, and median, mean, mode, 10th, 25th, 50th, 75th, and 90th percentile, and SD for a total of 100 parameters. Only data collected during the time interval 9:00 P.M. to 9:00 A.M. with a minimum of 20 minutes of device data recording and with no missing data on any of the 100 parameters were included in the analysis.

Statistical Analysis

The random forest (RF) method was used to assess the strength of association between the device variables and report of asthma symptoms. RF is a supervised statistical learning method for classification (23). RF was used to build a prediction model using the variables derived from the device to predict the presence of asthma symptoms each night. RF was performed on the analytic cohort after excluding the time period 14 days before the date of symptom onset and 14 days after the date of symptom resolution and all other time periods where outcome was missing as the training set. Based on the minimization of the out-of-bag error rate, the optimal parameter of the RF models were 70 variables at each node, and the forest included 2,000 trees. The leave one out validation (*n*-fold cross validation) method was used to determine the performance of the model. The importance of each variable in the model was determined by averaging each tree error after permuting randomly the values of that variable on the out-of-bag records. In addition, RF was conducted on two individual patients—subject 3 and subject 10—as it was hypothesized that results could vary considerably among subjects, and performance may change when including single subjects. These two subjects were selected as they had more than 100 nights of device data recording and at least 20 nights during which the outcome (reported symptoms) occurred.

Prediction

The performance of the RF algorithm was assessed regarding prediction of asthma symptoms on our test set which consisted of

Figure 2. Model prediction of asthma during the 14 days before reported asthma symptoms for all subjects with asthma symptoms. The random forest model was applied to data from days preceding report of asthma symptoms to evaluate ability of the model to predict asthma before it was reported by the subject. On the day before report of symptoms, the model predicted loss of asthma control in 35% of cases tested.

the 14 days before each date of asthma symptom onset where the symptom outcome status was coded as unknown. Because this two-week interval was not included in the training set, this data did not influence the model. The prediction of asthma symptoms was determined on the subset of patients with any asthma symptoms and on subjects 3 and 10.

Elastic Net Regression

Device output variables were additionally selected that were associated with ACT score using the elastic net shrinkage regression method. Given the high number of device parameters and the high level of correlation among some of the parameters, a combination of the least absolute shrinkage and selection operator and ridge regression methods, called elastic net, was chosen to correct for the potential interdependence of these variable (24). The parameters of elastic net regression were optimized using cross-validation. The elastic net regression was adjusted on patient identification to account for the average ACT value for each patient. ACT score was assumed to be constant for the 14- to 28-day period before (time between obtained ACT scores) score collection. In addition, bivariable analysis using a linear regression model was performed to understand the relationship between each

predictor variable and the ACT score adjusted for the patient identification.

All analyses were performed using SAS 9.4 (SAS Institute Inc.) and R 3.3.2 (The R Foundation for Statistical Computing).

Results

A total of 33 subjects were enrolled in the study; 16 had at least 2 survey collections and reliable nightly data, meeting criteria for data analysis (Table 1). Data available for analysis for each subject varied based on length of study participation and quality of data received (Table 2). As shown in Table 2, asthma symptom status of a given subject was not known for all nights of recorded physiologic data. There were 891 nights of nightly data, of which 161 nights were associated with asthma symptoms, used to generate the main RF model. In the main analysis using the training set, the RF model detected asthma symptoms with a sensitivity of 47.2%, a specificity of 96.3%, and accuracy of 87.4% (Table 3). The relative influence of the top five most important physiologic variables in the accuracy of the RF model is shown in Figure 1. The strongest predictor of asthma symptoms in the model was the mean HR, followed by the 90th percentile, 75th percentile, SD, and 25th percentile of HR. Statistical parameters of RR

fell in the top 20 most important variables in model prediction.

The performance of the RF model was additionally assessed individually for subject 3 and subject 10. Large differences in sensitivity of the model were found among subjects, such that the model was much more sensitive with certain subjects (Tables 4 and 5). The RF model for subject 3 performed with 77.1% sensitivity, 90.9% specificity, and 85.5% accuracy, whereas, for subject 10, it performed with 38.1% sensitivity, 94.2% specificity, and 84.7% accuracy. (Tables 4 and 5). There was little change in specificity or accuracy for the subjects evaluated.

The results of the prediction of symptoms during the 14 days before asthma onset are shown in Figure 2 and Table 6. Among the subset of subjects who experienced asthma symptoms during follow-up ($n = 10$), the model predicted asthmatic episodes 35% of the time on the day before the onset of symptoms, as perceived by the subjects, suggesting detectable changes in the device output variables before the report of asthma symptoms. For subject 3 (Figure 3, Table 7), with significantly higher model sensitivity, the model predicted asthma symptoms 100% of the time on the 2 days before a reported symptomatic period, with down-trending prediction in the days before the event.

Table 6. Random Forest Method Applied to 14 Days Before Onset of Asthma Symptoms for All Subjects with Asthma Symptoms

Days before Asthma Symptoms	Nights Model Does Not Predict Asthma	Nights Model Predicts Asthma
1	17 (65.38)	9 (34.62)
2	14 (66.67)	7 (33.33)
3	14 (63.64)	8 (36.36)
4	13 (72.22)	5 (27.78)
5	18 (75.00)	6 (25.00)
6	16 (72.73)	6 (27.27)
7	17 (77.27)	5 (2.73)
8	17 (80.95)	4 (19.05)
9	14 (73.68)	5 (26.32)
10	13 (68.42)	6 (31.58)
11	13 (68.42)	6 (31.58)
12	13 (72.22)	5 (27.78)
13	12 (75.00)	4 (25.00)
14	12 (80.00)	3 (20.00)

Data are presented as n (%).

The elastic net shrinkage regression method was used to identify physiologic variables associated with change in ACT score. In the multivariable analysis, the following variables showed an association with change in ACT score: median HR; mode HR; mode RR; 10th percentile of RR; 25th percentile of RR; 10th percentile of HRV; 75th percentile of HRV; 10th percentile of RRV; 25th percentile of RRV; 10th percentile of HR based on percentile for age; 25th percentile of RR based on percentile for age; 75th percentile of RR based on percentile for age; mode of relative Q; SD of relative Q; SD of the proxy for $\dot{V}O_2$; and median movement (Table 8). In the bivariable analysis, the following physiologic variables showed a significant independent association with ACT score: median HR; mode HR; mode RR; 25th percentile of RR; 75th percentile of HRV; 10th percentile of HR based on percentile for age; and mode of relative Q. The trend of inverse correlation of ACT score and median, 10th percentile, and 90th percentile HR and RR over time for a single subject, subject 16, are shown in Figures 4 and 5. Subject 16 is used as an example, given the relatively large number of nights of reliable data and fluctuations in ACT score.

Discussion

To the best of our knowledge, this is the first article to show that passive physiologic monitoring can be used in the home to assess asthma control. Physiologic monitoring provided sensitive and objective data that detected an asthma exacerbation and, in more than one-third of the episodes, did so even before children or parents recognizing the worsening symptoms. These results represent proof of concept that passive home physiologic monitoring is feasible in children with asthma, and can provide real-time data on asthma control. These results suggest that passive monitoring can generate objective information that is not limited by either interobserver variability or effort-dependent measurements. To more clearly identify the physiologic parameters most closely associated with report of asthma symptoms, an RF model was created. Increases in HR parameters were consistently associated with loss of asthma control. In up to 35% of instances, the model generated was able to predict loss of asthma control before the subjects' perception of symptoms. Moreover, HR and respiratory parameters correlated with changes in ACT score.

The RF model developed performed with high specificity and accuracy, but the

Table 7. Random Forest Method Applied to 14 Days Before Onset of Asthma Symptoms in Subject 3

Days before Asthma Symptoms	Nights Model Does Not Predict Asthma	Nights Model Predicts Asthma
1	0 (0.00)	4 (100.00)
2	0 (0.00)	3 (100.00)
3	2 (50.00)	2 (50.00)
4	0 (0.00)	3 (100.00)
5	2 (50.00)	2 (50.00)
6	3 (60.00)	2 (40.00)
7	5 (83.33)	1 (16.67)
8	4 (66.67)	2 (33.33)
9	3 (75.00)	1 (25.00)
10	3 (75.00)	1 (25.00)
11	2 (50.00)	2 (50.00)
12	2 (40.00)	3 (60.00)
13	4 (80.00)	1 (20.00)
14	3 (60.00)	2 (40.00)

Data are presented as *n* (%).

sensitivity of the model was low. One possible explanation for the limited sensitivity is that nocturnal physiologic changes may not occur with relatively minor asthma symptoms, and only more significant events cause physiologic changes. Alternatively, symptoms attributed to asthma by subjects may derive from other causes. Interestingly, the sensitivity of the model was better with certain subjects, suggesting differences between subjects in either perception of symptoms or physiologic response. Larger studies are needed to determine the cause of this variability.

Asthma management would likely be improved by the availability of reliable and objective indicators of asthma control that might be readily obtained in the home environment. The current pediatric asthma management guidelines are based largely on symptom report by patients and their family members, and yet symptom report is flawed (25–27). Spirometry and even peak flow can be technically difficult for children to perform accurately, and FEV₁ does not necessarily predict asthma severity (26). The difficulties in assessing asthma control pose a unique challenge to the development of scalable technology and services that can be delivered outside the home. Internet-based telemonitoring with portable spirometry has been studied with success in adults with asthma, although data in children are limited (28–30). Other home

Figure 3. Model prediction of asthma during the 14 days before symptoms reported for subject 3. The random forest model was applied to data from subject 3 alone from days preceding report of asthma symptoms to evaluate ability of the model to predict asthma before perception of symptoms. The model predicted loss of asthma control 100% of the time on the 2 days before the report of onset of asthma symptoms.

Table 8. Physiologic Variables Associated with Change in Asthma Control Test Score

Variables	Multivariable Analysis*	Bivariable Analysis [†]	P Value
HR median	−0.0739	−0.0680	<0.0001
HR mode	−0.0280	−0.0622	<0.0001
RR mode	−0.0315	−0.0622	<0.0001
RR 10th%	0.00732	−0.0525	0.3173
RR 25th%	−0.0412	−0.1109	0.0235
HRV 10th%	−0.0014	0.0061	0.1005
HRV 75th%	0.0009	0.0066	0.0044
RRV 10th%	0.0015	0.0002	0.9442
RRV 25th%	0.0005	−0.00003	0.9758
HRP 10th%	0.0129	−0.0201	0.0227
RRP 25th%	0.002608	−0.00565	0.6432
RRP 75th%	0.008374	−0.00294	0.4946
RQ mode	0.003087	0.01772	0.027
RQ SD	0.002987	0.03558	0.2239
RV _{O2} SD	0.000472	0.000271	0.8577
Movement median	0.000629	0.0006	0.1943

Definition of abbreviations: HR = heart rate; HRP = heart rate percentile for age; HRV = heart rate variability; RQ = relative Q; RR = respiratory rate; RRP = respiratory rate percentile for age; RRV = respiratory rate variability; RV_{O2} = relative V_{O2}.

*Using elastic net.

[†]Linear regression adjusted by patient.

Figure 4. Asthma control test (ACT) score and nocturnal heart rate (HR) over time in subject 16. The trend ACT score and median, 10th percentile, and 90th percentile HR over time for subject 16 are shown. ACT score is shown by the black line, median HR is shown by the dashed line, and the gray area reflects range of HR from 10th to 90th percentile. Decreases in ACT score, indicative of loss in asthma control, were mirrored by elevations in HR.

devices include wheeze detectors, which so far have only been studied in the inpatient setting, and wearable devices (31). Although wearables have the potential to provide a broad range of physiologic detail, they are inherently limited by the virtue that they must be worn, and there are a lot of confounding variables during the day that may make data analysis challenging. Similarly, home spirometry, peak flow, exhaled nitric oxide, or wheeze detectors must be used regularly by the patient to be effective. In a field in which adherence is already an issue, increasing the compliance burden may not represent an optimal strategy. Passive asthma monitoring is the next frontier, and may be the answer to eliminating the biases in perception of asthma control.

Our study suggests that nocturnal changes in HR and RR may be objective metrics that can be used to assess asthma control in the home environment. Data surrounding changes in HR and RR before an asthma exacerbation are limited, owing in part to the challenges of measuring physiology parameters in the home environment. One relatively recent study demonstrated a change in peak expiratory flow up to 2 weeks before an asthma exacerbation, although earlier work suggested that symptom diary may be more sensitive (18, 32). Another report demonstrated that cough can be passively measured and that frequency of nocturnal cough correlates with asthma control (19). Thus, it is not surprising that physiologic changes occur with loss of asthma control, but the finding that HR better reflected asthma control than RR in both the RF and elastic net regression analyses was unexpected.

Albuterol use may not be the primary explanation for the nocturnal increase in HR for several reasons. First, these data derive from times when the subject was in bed and likely sleeping, presumably well after last albuterol use. In support of this interpretation, the 25th percentile HR for a given evening was associated with report of symptoms, in addition to the mean, and 75th and 90th percentiles. The lower-percentile HRs are most likely to reflect the times when the subject was asleep (33). Moreover, studies of albuterol use in pediatric patients have shown only small increases in HR with single dose of albuterol, and with treatment of asthma exacerbations, HR declines (34–36). Finally,

Figure 5. Asthma control test (ACT) score and nocturnal respiratory rate (RR) over time in subject 16. The trend ACT score and median, 10th percentile, and 90th percentile RR over time for subject 16 are shown. ACT score is shown by the black line, median RR is shown by the dashed line, and the gray area reflects range of RR from 10th to 90th percentile. Decreases in ACT score, indicative of loss in asthma control, were mirrored by elevations in RR.

the RF model possesses the capacity to predict asthma events before report of symptoms, suggesting changes in physiologic before either the use of albuterol or perception of symptoms by the subject. From this study, we now know that not only do changes in physiologic parameters occur with loss of asthma control, but also that increases in nocturnal HR and RR correlate with asthma symptoms. Furthermore, in some cases, these changes can precede the perception of asthma symptoms.

There are several limitations to this study. The sample size was small, and several subjects had significantly more nights of usable data than others. These factors may limit the generalizability of the findings. In addition, the analysis of ACT score required the assumption that ACT score was constant over the preceding 2- to 4-week interval, thus introducing significant noise into the analysis. This may account for some of the quantitative differences in the statistical measures of each physiologic variable associated with asthma control as

compared with the RF analysis. The RF and the elastic net regression analyses came to the consistent conclusion, however, that HR and RR parameters showed the strongest association with asthma symptoms.

The present study demonstrated that either nocturnal HR or RR correlate with worsening of asthma control. The association between asthma control and objective physiologic parameters has the potential to provide reliable and objective outcome measures to monitor asthma control longitudinally. Strategies that enable monitoring in the home environment, especially those that entail almost no participation from the subject other than sleeping in his or her own bed, represent a novel, potentially scalable solution to the conundrum of asthma management. The prediction models presented here can be tailored to the individual through machine learning methods, bringing the paradigm of machine learning to the management of a common childhood disease. This technology may be particularly helpful in the challenge of predicting loss of control in subjects with poor perception of symptoms and those with exacerbations after long periods of control, and may additionally reveal that subjects with frequent exacerbations never truly achieve control between episodes. Use of objective measures in concert with home monitoring of asthma will enable health care providers to more accurately track asthma control over time rather than rely on patient recall and the snapshot of objective measures obtained during a clinic visit. This strategy has the potential to detect the onset of asthma exacerbations even before patients or parents appreciating an impending worsening of asthma control. Further studies are needed to determine if nocturnal physiologic monitoring can be used to not only detect an exacerbation, but might be able guide intervention and improve asthma control. ■

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