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Heart Rate Variability in Children With Obstructive Sleep Apnea

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Summary: Adults with obstructive sleep apnea syndrome (OSAS) display substantial heart rate changes associated with obstructive events, and recent reports suggest similar heart rate changes in children with OSAS. These rate changes could assist screening of young patients for OSAS. Six-hour polysomnographic recordings were obtained from seven children with OSAS (mean age: 4.5 years; apnea index: 19.5 ± 5.1) and from seven primary snorers without OSAS who served as controls (mean age: 4.7; apnea index: 0). Scatterplots of each cardiac R–R interval against the preceding interval (Poincaré plots) were used to assess beat-to-beat cardiac variability at different heart rates. Beat-to-beat variation at slow rates was significantly increased in children with OSAS relative to controls, while variation at fast and intermediate heart rates was significantly reduced in these children. We conclude that OSAS alters beat-to-beat variation in characteristic fashions in children, that the variability changes occur at all heart rates but are most significant at slow heart rates, and that these heart rate patterns could assist in screening of suspected cases of OSAS. **Key Words:** OSAS—Respiration—Upper airway obstruction—Autonomic nervous system.

Obstructive sleep apnea syndrome (OSAS) is a relatively common syndrome in pediatric patients (1). Although obesity is not as significant a contributing factor in children as in adults (1), adenotonsillar hypertrophy and other medical conditions that preferentially afflict children result in a substantial incidence of sleep-disordered breathing. Identification of suspected OSAS in pediatric patients normally requires an all-night sleep recording to identify instances of obstructed events and to document accompanying sequelae. The substantial cost and inconvenience of prolonged polysomnographic recordings frequently preclude routine evaluation for the syndrome, heightening the potential for failed detection of the condition and causing needless concerns for a non-existing syndrome in otherwise normal children who snore. A need exists for description of outstanding physiologic characteristics associated with obstructive sleep apnea in pediatric patients so that simple, non-invasive screening tests can be developed for children with suspected OSAS before more thorough evaluations are conducted on candidates likely to be afflicted.

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The most obvious physiologic assessment would directly measure breathing or oxygen saturation characteristics during sleep. However, easy assessment of both thoracic excursion and airflow has thus far eluded sleep researchers; difficulty in transducer placement, substantial interference from movements, transducer failure, difficulty in separation of respiratory measures from other sources, and other artifacts have hindered screening efforts. Nocturnal oximetry has been only partially successful in screening in adults (2). Other physiologic changes that accompany cessation of breathing may provide useful identification of OSAS.

Adult OSAS results in substantial alterations in cardiac beat-to-beat variability as well as a significant incidence of arrhythmia (3–5). The extreme sensitivity of respiratory action to transient blood pressure changes (6,7) and the close integration of breathing on cardiovascular action (8) suggest that concomitant cardiovascular activity associated with apneic events would be useful in identifying the occurrence of disordered breathing. Indeed, characteristic tachycardia sequences have long been associated with adult apneic episodes (5), and heart rate and variability changes also occur during obstructive events in children (9). The possibility exists that easy-to-measure assessments of cardiac interval variation might show characteristic

patterns in pediatric patients with obstructive sleep apnea thus allowing preliminary screening for the syndrome.

The objective of this study was to assess beat-to-beat cardiac interval variation during sleep in pediatric patients with documented obstructive sleep apnea relative to normally breathing subjects so as to determine if cardiac interval variation characteristics were consistently unique in the OSAS group. Unique characteristics would provide insights into the nature of hemodynamic responses to obstructive apnea and have the potential for development of screening tools that use an easy-to-measure physiological aspect, the electrocardiogram (ECG). Assessment of variation included procedures that have been useful in evaluating cardiac beat-to-beat variation in normal and diseased infants and children (10–13).

SUBJECTS AND METHODS

Subjects

The sample consisted of 14 children, with histories of snoring, referred to Childrens Hospital Los Angeles between July 1993 and February 1995. The experimental group consisted of seven children (two female, five male) with polysomnographic findings of obstructive sleep apnea associated with desaturations below 90%. All seven of these children were diagnosed with adenotonsillar hypertrophy. None of the patients had history or signs of chronic lung, cardiac, or neuromuscular disease, and none were on medication at the time of the study. The control group consisted of seven otherwise health children (five female, two male) with complaints of snoring but normal polysomnograms.

These data were gathered in the course of clinically indicated polysomnograms with no impact on the subjects. Therefore, Institutional Review Board approval was not necessary.

Sleep studies

Overnight polysomnographic studies were performed without sedation or sleep deprivation. All children were accompanied by one parent throughout the study. The following parameters were recorded continuously on a Gould 16-channel stripchart recorder at a paper speed of 10 mm/second (Gould Instruments, Rolling Meadows, IL):

1. Ribcage and abdominal respiratory effort by uncalibrated respiratory inductance plethysmograph (Ambulatory Monitoring, Ardsley, NY).
2. Inspired and end-tidal PCO_2, sampled at the nose or mouth at a rate of 60 ml/minute by mass spectrometry (Perkin-Elmer Medical Gas Analyzer, Perkin-Elmer Medical Instruments, Pomona, CA).
3. Airflow, sampled at the opposite site with a thermistor (Physitemp, Clifton, NJ).
4. S_PO_2 by pulse oximetry (Nellcor N 200 Pulse Oximeter, Hayward, CA).
5. Oximeter pulse waveform.
6. Transcutaneous PO_2 and PCO_2, using a heated (43°C) transcutaneous oxygen electrode (Sensormedics Transend Cutaneous Gas System, Sensormedics, Yorba Linda, CA). Trends of transcutaneous values were used to confirm the $P_{ET}CO_2$ and oxygen saturation levels. Transcutaneous electrodes were moved every 4 hours to prevent irritation of underlying skin.
7. Electroencephalograph (EEG) with central (C3–C4) and auricular electrodes.
8. ECG (electrodes placed at the right and left second intercostal spaces at mid-clavicular lines, 1 cm below the ribcage at the left anterior-axillary line). Electrooculograph (EOG) and chin electromyograph (EMG) with standard surface electrodes.

PCO_2, thermistor airflow, S_PO_2, and oximeter pulse waveform were digitized at sample rates of 62, 62, 125, and 125 samples per second, respectively, and stored on optical media. ECG was fed to a trigger generator that produced a pulse for each R-wave, and the time of each R-wave (accurate to 1 msecond) was stored with the digitized data. EEG, EOG, and EMG were used only to identify waking periods to compute apnea indices, and, as such, these signals were not digitized.

Children were continuously observed by a technician and recorded on videotape by an infrared videocamera. Observations of the child's sleep behavior and respiratory events were recorded directly on the stripchart paper by the technician.

Obstructive sleep apnea was defined as the presence of chest wall motion associated with absence of airflow detection by both the end-tidal catheter and thermistor. The obstructive apnea index was determined for each recording as the numbers of obstructive apnea of any length per hour of sleep.

Measurement of intervals between successive R-waves of the ECG (R–R intervals) were calculated from R-wave trigger times with an accuracy of ±1 msecond. Artifactual R–R intervals were corrected by an automated artifact identification and correction routine. This routine identified artifacts as R–R intervals dramatically different from the preceding three intervals. Excessively large R–R intervals were assumed to be missed triggers and were corrected by dividing the long interval into two or more intervals of more appropriate lengths. Extremely short intervals were con-

TABLE 1. *Mean values ± standard deviation (SD) and ranges for anthropometric data in seven normal children and in seven children with OSAS*

	Age (years)	Weight (kg)	Weight (%)	Height (m)	Height (%)	BMI (kg/m²)
Normals	4.7 ± 1.9 (2–8)	19.5 ± 4.8 (12–27)	65 ± 17 (40–85)	1.1 ± 0.13 (0.8–1.3)	62 ± 22 (25–90)	17.0 ± 1.2 (14–19)
OSAS	4.5 ± 2.2 (1–6)	19.1 ± 7.4 (12–32)	61 ± 30 (20–95)	1.0 ± 0.18 (0.8–1.4)	57 ± 33 (10–95)	16.8 ± 1.3 (15–18)
p value	0.5	0.4	0.4	0.4	0.4	0.4

BMI, body mass index. BMI (weight/height²) is an indirect measure of obesity and correlates with more direct measures of adiposity such as hydrostatic weighing and other techniques (14). Percentile scores for weight and height are based on National Center for Health Statistics growth charts (15).

sidered to be double triggers and corrected by adding the short interval to a neighboring short interval to create one interval comparable to the surrounding intervals. Each R–R interval was plotted against the previous R–R interval to produce individual scattergrams (Poincaré plots) for each child, and these plots were examined visually for patterns of change that might identify pathologic conditions.

For each recording, dispersion of next-intervals was determined following short (10th percentile), long (90th percentile), and intermediate (50th percentile) R–R intervals. Short intervals (10th percentile) reflect fast heart rates; thus, dispersion of intervals following short intervals indicates beat-to-beat heart rate variability when heart rate is fast. Correspondingly, dispersion following intermediate (50th percentile) and long (90th percentile) R–R intervals reflects beat-to-beat heart rate variability at intermediate and slow heart rates, respectively. At each R–R interval level (10th, 50th, and 90th percentile), dispersion was quantified as the range of next-interval values. Because the range of values could be profoundly affected by one or two outlying values, the highest and the lowest 1% of next-interval values were eliminated before dispersion was computed.

Data analysis

Repeated-measures analysis of variance (ANOVA) and student *t* tests were used to compare dispersion of R–R intervals in the two groups (OSAS vs. normal) at the 10th, 50th and 90th percentiles of R–R intervals (fast, intermediate, and slow heart rates, respectively). Because heart rate variability is dependent on basal heart rate, an additional ANOVA introduced mean heart rate of each child as a covariate. A p value of <0.05 was adopted as statistically significant.

TABLE 2. *Mean values ± SD and ranges for sleep–respiratory parameters in seven normal children and in seven children with OSAS*

	Apnea index	Mean saturation (%)	Mean $P_{ET}CO_2$ (mm Hg)
Normals	0	98.8 ± 0.8 (97.1–99.3)	42.5 ± 2.8 (37.6–46.4)
OSAS	19.5 ± 5.1 (13.9–22.5)	91.9 ± 2.3 (86.0–94.1)	45.4 ± 2.3 (40.4–48.9)
p value	<0.0005	<0.0005	<0.05

Apnea index, number of obstructive apneas of any length per hour of sleep.

RESULTS

Anthropometric data

Anthropometric information about the two groups of children is provided in Table 1; *t* tests showed no significant differences between the two groups. Total sleep time did not significantly differ in the children with OSAS vs. control children, and proportions of time spent in stage 1/2, stage 3/4, and REM sleep were similar in the two groups of children.

Respiratory data

Respiratory measures in the control children and children with OSAS are indicated in Table 2. Children with OSAS showed significantly higher mean apnea index ($p < 0.0005$) and significantly lower mean saturation ($p < 0.0005$) when compared to the controls (primary snorers with normal polysomnograms). The affected children also showed a significant increase in mean $P_{ET}CO_2$ values relative to the controls ($p < 0.05$); however, the difference in $P_{ET}CO_2$ was small and is probably not of clinical significance.

Beat-to-beat heart rate variability

Plots of R–R intervals from a period of steady respiration in a control child and during obstructive episodes in a child with OSAS are shown in Fig. 1. Children with OSAS showed reduced R–R intervals (faster heart rate) beginning a few seconds after initiation of obstruction, followed by increased R–R intervals (slower heart rate) with greatly enhanced variation when breathing resumed.

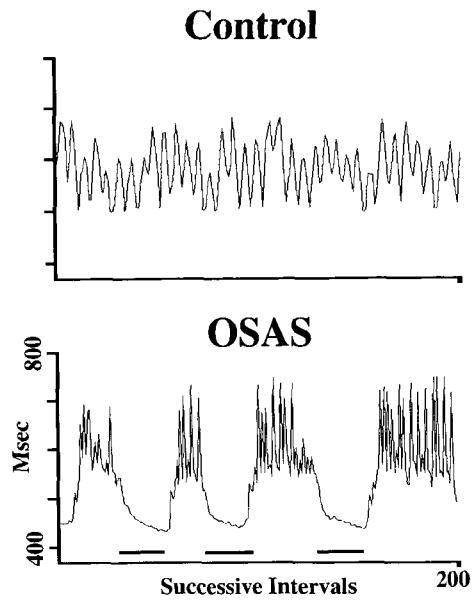

FIG. 1. R–R intervals in one primary snorer without obstructive sleep apnea syndrome (OSAS) (control) and in one patient with OSAS. During obstructive apnea (indicated by solid bars), a decrease in R–R intervals (reflecting increased heart rate) occurred. Enhanced high-frequency heart rate variation followed the apneic events. Note that the x-axis is measured in R–R intervals and does not reflect a linear measure of time.

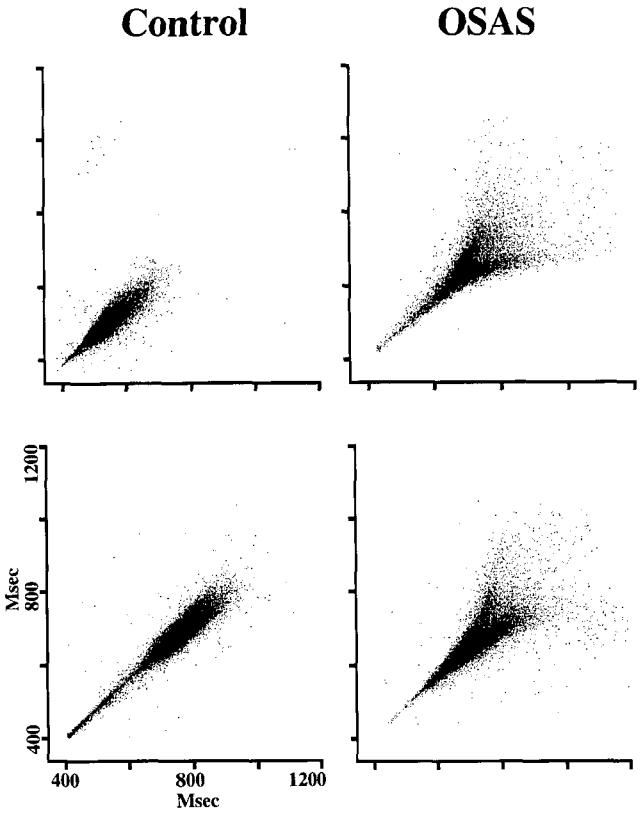

FIG. 2. Poincaré plots from two primary snorers without OSAS (controls) and two children with OSAS. Note the wide, bimodal scatter observed in children with OSAS at long R–R intervals (corresponding to low heart rates).

Poincaré plots of normal children and children with OSAS are shown in Fig. 2. These plots demonstrate several aspects of heart rate dynamics. The dispersion of points on the x-axis represents the overall variation, and the extent of dispersion along the y-axis at a given x-value represents the beat-to-beat variability following an R–R interval of a given duration. The Poincaré plots derived from each subject showed an overall linear correlation (Pearson's R, $p < 0.005$ in every case) as illustrated by the positive diagonal scatter of points.

Poincaré plots of children with OSAS showed markedly different patterns from those of controls. The Poincaré plots of children with OSAS tended to show much greater next-interval dispersion following long R–R intervals (slow heart rates) than did those of control children.

Mean beat-to-beat dispersion in children with OSAS and controls following intervals at the 10th, 50th, and 90th percentiles are shown in Fig. 3. The overall analysis showed a highly significant interaction between the presence of OSAS and a measure from the scatterplots, the length of the previous R–R interval (10th, 50th, or 90th percentile; $p < 0.005$). Analysis of simple effects showed that next-interval dispersion following short (rapid heart rate) and intermediate R–R intervals was significantly reduced in children with OSAS relative to controls ($p < 0.05$ in each case). Next-interval dispersion following long R–R intervals (slow heart rates), however, was significantly greater in the OSAS children than in controls ($p < 0.0005$).

The addition of basal heart rate as a covariate in the analysis showed that differences in basal heart rate had

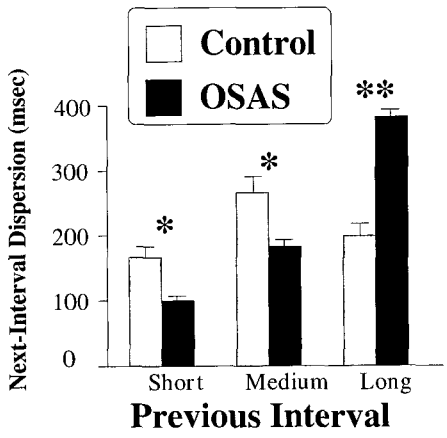

FIG. 3. Mean next-interval dispersion following short, intermediate, and long R–R intervals in primary snorers without OSAS (controls) and children with OSAS. Children with OSAS showed significantly reduced next-interval variation following short and intermediate R–R intervals but significantly enhanced variation following long intervals. Single asterisks indicate differences significant at $p < 0.05$; ** indicates differences significant at $p < 0.0005$. Bars indicate standard errors.

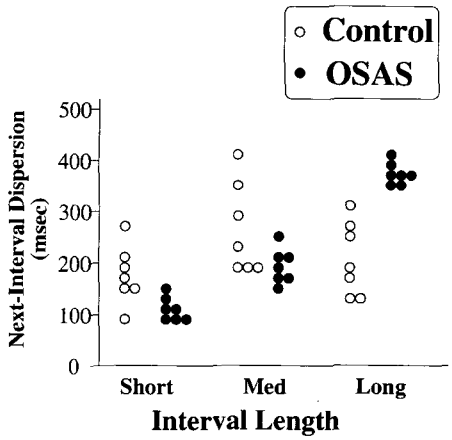

FIG. 4. Next-interval dispersion in each subject following short, intermediate (Med), and long R–R intervals. Although there is some overlap of control and OSAS values following short and intermediate R–R intervals, the two groups showed no overlap in dispersion values following long intervals. (Controls are primary snorers without OSAS.)

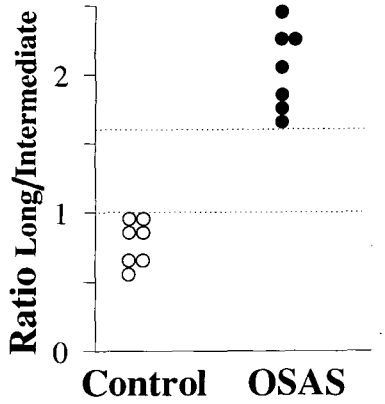

FIG. 5. Ratio of next-interval dispersion following long vs. intermediate R–R intervals in primary snorers without OSAS (controls) and children with OSAS. This ratio did not exceed 1.0 in any of the control children yet was above 1.6 in all subjects suffering from OSAS. This measure showed a highly significant difference between the two groups of children ($p < 0.0005$).

no effect on next-interval dispersion ($p > 0.10$); partitioning heart rate effects, therefore, had no effect on the findings. There was no difference in heart rate between the two groups of children ($p > 0.10$) and overall heart rate variability, as assessed by the difference between the 90th percentile R–R interval and the 10th percentile R–R interval, was also comparable in the two groups of children ($p > 0.10$).

Dispersion following short, intermediate, and long intervals in each child is shown in Fig. 4. The controls showed an increase in dispersion as the previous interval increased from short (10th percentile) to intermediate (50th percentile) and then a small reduction in dispersion as the length of the previous interval further increased to the 90th percentile (long). Children with OSAS tended to have lower dispersion than did the controls following short and intermediate R–R intervals, but the increase in dispersion from short to intermediate intervals was proportional to that observed in the controls. However, unlike the control children, children with OSAS showed a profound increase in dispersion as the length of the previous interval increased from the 50th to the 90th percentile. Following long R–R intervals, there was no overlap in the dispersion values observed in control children and those with OSAS; in controls, next-interval dispersion following long R–R intervals ranged from 130 to 301 mseconds, whereas, the lowest value for this dispersion in the OSAS group was 351 mseconds.

The findings that dispersion increased from the 50th to the 90th percentile in children with OSAS but decreased over that range in control children (see Figs. 3 and 4) suggest that the ratio of one to the other may differentiate between the two groups of children better than either raw dispersion value. The ratio of dispersion following long vs. intermediate intervals is shown for each child in Fig. 5. This ratio did indeed separate the two groups of children, the largest ratio in the normal group being 0.9; while the ratios in the children with OSAS ranged from 1.6 to 2.4. A post hoc ANOVA of this ratio predictably showed a highly significant difference between the two groups of children ($p < 0.0005$).

A further post hoc analysis was done to determine if, within the OSAS group, severity of respiratory disturbance was correlated with the degree of dispersion at any heart rate. Pearson's *R* showed no significant correlation between apnea index and any measure of dispersion ($p > 0.05$ in each case) in the seven children with OSAS.

DISCUSSION

Children with OSAS show distinct patterns in cardiac R–R interval variation, with enhanced beat-to-beat variation at lower heart rates and reduced variation at faster rates relative to control children. However, because heart rate variation in the OSAS children was enhanced at times and diminished at others, overall heart rate variation was not significantly affected. This paradox demonstrates how differences in heart rate patterning can be missed in examination of overall variability and highlights the importance of examining characteristics of beat-to-beat patterns of heart rate.

The origin of aberrant Poincaré patterns can be seen by examination of R–R interval sequences surrounding obstructive events (see Fig. 1). During an obstructive apnea, heart rate increases, and, although the overall change in heart rate from the beginning of the apneic period to its termination may be substantial, the changes in interval length from one beat to the next

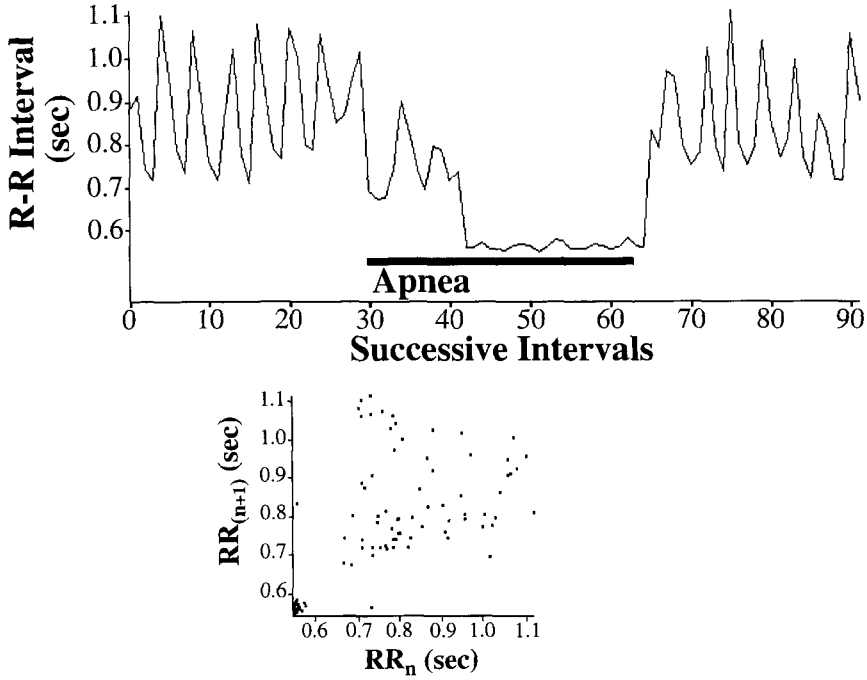

FIG. 6. A plot of R–R intervals surrounding an obstructive event and the resulting Poincaré plot. Heart rate is fast and fixed during the obstruction and slow and highly variable before and after the event as a result of rebound bradycardia following the previous apnea and the apnea shown. Note that the tachycardia during the obstruction results in a very tight cluster of points in the lower-left corner and the rebound bradycardias are reflected by widely scattered points to the right.

are extremely small; thus, following short R–R intervals (fast heart rates), beat-to-beat changes are reduced in children with OSAS. When the apneic episode is over, however, a profound heart rate deceleration and pronounced respiratory arrhythmia ensue, most likely precipitated by rebound vagal outflow associated with baroreflex action accompanying the episode. During the heightened oscillatory activity at slow rates, changes from one R–R interval to the next are often substantial, resulting in Poincaré plots displaying enhanced variation at slow heart rates. Moreover, the V-shaped nature of the Poincaré plots at slow rates indicates that these long intervals are rarely followed by other intervals of comparable length (which would be reflected by points along the line of identity) but are usually followed by much shorter intervals (indicated by points in the lower right of the plot) or much longer intervals (points in upper left). This V-shape distribution of points with few points in the center is qualitatively different from distributions seen in primary snorers and normal children (13).

A Poincaré plot from a small section of R–R intervals (Fig. 6) demonstrates that tachycardia during obstruction is reflected by a very tight cluster of points in the lower-left corner and the subsequent bradycardia is reflected by widely scattered points in the upper right. The tight cluster of points at a very high heart rate and wide scatter of points at low rates can account for the reduced dispersion at fast and enhanced dispersion at slow rates, respectively, in children with OSAS.

An important aspect of these findings is that altered patterns of dispersion are apparent even if intervals are collapsed across all sleep states over a night. This finding has substantial implications for determination of physiological signs useful for screening of children suspected of having OSAS. Sleep state has profound effects on heart rate patterning, and partitioning of sleep state, therefore, offers substantial insights into the nature of the obstructive processes. However, differentiation of state may be difficult or impossible during conditions of repetitive apneic events, and assessment for potential OSAS would be useful in the absence of sleep-state differentiation. Determination of Poincaré patterns from cardiac R–R intervals is a trivial computation task and provides, in a single plot, an overall view of several characteristics of cardiac interval variation over a long recording.

Analysis of overnight heart rate patterning across all sleep–waking states combined introduces the possibility that differences between groups of children may emerge from differences in sleep state distributions (e.g. more arousals or reduced active sleep in OSAS subjects). However, sleep state distributions were comparable in the two groups of children; moreover, the altered distribution of points in plots of children with OSAS corresponds to alterations in patterning of R–R intervals accompanying apnea. In particular, the mark-

edly increased dispersion at low heart rates that reflects greatly enhanced high-frequency, respiratory-related heart rate variation cannot be accounted for by simply a change in sleep state distribution.

A previous study of cardiac R–R interval variation found that overall R–R interval variability changes in children with OSAS were modest, with the magnitude of absolute changes showing a mean decline of only 5.3% (9). These investigators argued, therefore, that the minimal change in overall R–R interval variation could not be reliably used for screening of severity of OSAS or blood gas abnormalities. We also found minimal or no difference in mean heart rate and overall variation in cardiac R–R intervals. However, controlling for aspects of heart rate while assessing variation demonstrates clear differences between children with OSAS and primary snorers with normal polysomnograms. The significant aspect of the present study is the capability to examine instantaneous variation at particular rates; that dimension allows significant differentiation between groups.

In this study, the subjects with OSAS had relatively severe sleep-disordered breathing. Children with more subtle abnormalities may have Poincaré plots that are more difficult to differentiate from controls. This technique should be evaluated in OSAS over the full spectrum of severity to determine its usefulness in identifying mild to moderate cases of OSAS.

It should be noted that other Poincaré patterns may be characteristic for other dysfunctions, such as momentary arousals resulting from periodic leg movement (16). Such events have the potential to modify cardiac interval variation and thus Poincaré plots in unique fashions. The range of heart rate variation that might emerge from other disorders of sleep have yet to be catalogued. However, obstructive sleep apnea results in characteristic scattergram patterns that can be distinguished from non-disturbed patterns; thus, the scattergrams provide a potentially useful screening technique that may be followed up with more detailed recordings.

We conclude that beat-to-beat heart rate patterns are considerably different in children with OSAS, relative to other children, and that beat-to-beat heart rate variability studies could, therefore, assist in screening of suspected pediatric cases of OSAS. The use of such a simple and inexpensive measure as a primary screening tool in suspected cases of pediatric OSAS could result in substantial savings of money and time and allow focusing of resources on those children who have the syndrome.

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