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Heart Rate Variability in Pediatric Obstructive Sleep Apnea

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***Abstract*—Obstructive sleep apnea syndrome (OSAS) is observed in approximately 2% of children. Heart rate variability (HRV) is a potentially simple, non-invasive diagnostic screening tool for OSAS. In this study, we investigated the diagnostic potential of HRV using power spectral analysis, numerical titration, sample entropy, and detrended fluctuation analysis. Effects of sleep stages (REM and NREM sleep) are evaluated. The results show that the heart rate chaos intensity, as measured by the noise limit in numerical titration, is significantly higher during REM sleep than NREM sleep in all patient groups. By using the receiver-operating characteristic analysis, the detection of OSAS yielded a specificity of 72.2% and sensitivity of 81.3% using the numerical-titration technique. The findings suggest that sleep state and disordered breathing are important determinants of cardiac autonomic control. Nonlinear techniques such as numerical titration, when used in conjunction with spectral analysis of HRV could be an effective screening tool for pediatric OSAS.**

***Index terms*—Heart rate variability, nonlinear dynamics, obstructive sleep apnea, pediatric**

I. Introduction

OBSTRUCTIVE sleep apnea syndrome (OSAS) is a common nocturnal breathing abnormality in which the airflow is impeded by a narrow upper airway despite continued respiratory efforts. Studies suggest that OSAS is an important risk factor for various complications such as cardiovascular diseases, arterial hypertension, myocardial infarction, hyperactivity and neurocognitive deficits [1]. OSAS reportedly affects 2 – 4% of children [2]-[3]. During obstructive apnea, increased respiratory effort leads to an increase in the negative intrathoracic pressure and an increase in the afferents inputs from the lungs and the chest wall to the autonomic nervous system (ANS), thus affecting cardiovascular autonomic control [4]. In addition, the termination of airway obstruction is frequently accompanied by sympathetic activation.

The gold standard for the clinical diagnosis of OSAS in children is polysomonography (PSG), consisting of simultaneous recordings of electrophysiological and respiratory signals, and overnight monitoring of the patient in a specially-equipped sleep laboratory. However, the scarcity of pediatric sleep clinics and the expense associated with standard PSG underestimates the number of pediatric OSAS cases. In addition, until recently, adult criteria were used to detect pediatric OSAS, producing inaccurate results [5]. Thus, a simple, less costly, noninvasive, reliable and ambulatory screening method for pediatric OSAS is desirable.

Analysis of heart rate variability (HRV), as indicated by the beat-to-beat fluctuation in the electrocardiogram (ECG) signal, has become an increasingly popular noninvasive approach for assessing cardiovascular autonomic control. The R-R interval (RRI)—the time between successive heart beats—is based mainly on two components: the intrinsic firing rate of the sinoatrial (SA) node of the heart and the regulation of the SA node firing rate by the collective inputs of the ANS. HRV can provide information on the relative inputs of the two ANS mutually antagonistic components—the sympathetic nervous system (SNS), which acts to increase heart rate, and the parasympathetic nervous system (PSNS), which acts to slow the heart, and dilate blood vessels [6]-[9].

Since HRV is an output of a deterministic system, i.e. the ANS, changes in HRV may reflect abnormalities in the system. This "deterministic" hypothesis of HRV has been the subject of intense investigation in recent years. Cyclical variation in heart rate was described as being characteristic of OSAS [10]. The unique heart rate rhythm of brady-tachycardia in OSAS [11] may provide the basis for an effective screening tool.

Standard spectral analysis of HRV can provide analytical features of its cyclic variation but cannot show the dynamical properties of the fluctuations. Furthermore, it has been shown that ANS control underlies the nonlinearity and possible chaos of normal HRV [12]. In the present study we aimed to systematically compare various time-series metrics for diagnosis and quantification of pediatric OSAS from electrocardiogram recordings alone. We also used the Wigner-Ville transform to perform a time-frequency domain analysis of the instant changes of autonomic control occurring during apnea episodes. In addition, we sought to examine the sleep-apnea severity in different sleep states.

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II. METHODOLOGY

A. Data Acquisition

The study consisted of 52 subjects: 16 were classified as severe/moderate OSAS, 18 are mild/borderline, and 18 are normal. All subjects underwent a standard nocturnal polysomnographic study at Johns Hopkins Hospital. ECG recordings, apnea events and sleep stages were acquired using Respironics Alice 3 Healthdyn Systems. All subjects were free of lung or neuromuscular disease, cardiac pathology or arrhythmia.

Obstructive apnea is defined as cessation of oronasal airflow in presence of respiratory efforts lasting longer than two respiratory cycle times. Hypopnea is defined as a discernible reduction in amplitude of oronasal airflow accompanied by a 4% oxygen desaturation and/or arousal. The apnea/hypopnea index (AHI) is defined as the number of apnea and hypopnea events per hour of sleep and a threshold of AHI $\geq$ 10 h^{-1} identifies children with OSA. The mean apnea-hypopnea index was 27.9 ± 2.8 h^{-1} for severe OSAS subjects, 12.02 ± 2.5 h^{-1} for moderate.

B. Signal Conditioning/Feature Extraction

Using the Alice 3 software, a continuous three-hour ECG recording was extracted for each subject. The three-hour recording also included at least one continuous 10-minute segment of each sleep stage: rapid eye movement (REM), stage-2 sleep and stage-4 sleep. The sleep stages were scored every 30 seconds. In addition, the three-hour recording captured apnea/hypopnea events consistent with the AHI of the OSAS patients.

The ECG was sampled at 100 Hz with 8-bit precision. The R-waves fiducial points were detected using a Hilbert transform-based peak extraction algorithm [13]. RRI was visually screened for artifacts, manual editing was performed to a very high standard. No attempt was made to distinguish normal sinus beats from ectopic beats. The beat-to-beat (R-R) interval (measured in milliseconds) time series was obtained by plotting the sequential intervals between beat *i* and beat *i*+1. The RRI time series was converted into equally spaced samples in time by cubic spline interpolation with a sampling rate of 4 Hz.

C. Analysis

1) Numerical Titration

Numerical titration [14] is currently the only algorithm available that provides a sufficient test for chaotic dynamics in noise-contaminated experimental time series. Rather than filtering the noise before chaos analysis, which could risk "bleaching" the chaotic dynamics [15], the numerical titration technique is analogous to a chemical titration: it measures chaos (acidity) by a controlled neutralization with added noise (base), thus allowing a "litmus test" for chaos.

Under the numerical titration scheme, the output noise limit (NL) > 0 indicates the presence of chaos, and the value of NL also gives an estimate of its relative intensity. Conversely, if NL = 0, then it may be inferred that the time series is either non-chaotic or the chaotic component has been neutralized by the noise floor in the data. Therefore, the condition NL > 0 provides a simple sufficient test for chaos.

In this study, numerical titration was applied on the RRI time series with a 5-minute-long window that slides at 30-second intervals.

2) Approximate Entropy and Sample Entropy

Approximate entropy (ApEn) is a statistical index that quantifies the unpredictability of fluctuations in a time series [16]-[18]. ApEn provides quantitative information about the complexity of experimental data that are often short and noise contaminated, and in many cases, have inherent dynamics that exhibit both deterministic and stochastic behaviors. ApEn reflects the logarithmic likelihood that two sequences that are similar (within a tolerance *r*) for *m* points remain similar at the next point. A time series that exhibits frequent and similar epochs has a relatively small ApEn value, reflecting a high degree of regularity.

ApEn is inherently biased because self matches are incorrectly counted to avoid the occurrence of logarithm of zero in the calculations; its expected value is not equal to the parameter it estimates. In addition, it has been suggested that this method may heavily depend on the data length and lacks relative consistency; that is, if ApEn of one data set is higher than that of another for one set of parameters *m* and *r*, it should, but does not remain higher for different parameters of *m* and *r* [19]. To correct for this inconsistency and to reduce bias, a variant of ApEn, known as sample entropy (SampEn), was introduced by Richman [19].

In this study, we computed ApEn and SampEn for each of the 5-minute segments of the heart-rate time series. We chose $m = 2$ and $r = 20\%$ of the standard deviation for the 5-minute segment. A mean value for entropy was obtained to characterize each segment.

3) Detrended Fluctuation Analysis

Detrended fluctuation analysis (DFA) [20]-[21] is a scaling analysis that quantifies long-range power-law correlation exponents in a signal. This technique is a modification of root-mean-square analysis of random walks applied to non-stationary data. Unlike the other statistics used in this study, which are based on the segmented RRI time series, the DFA index is based on the full length RRI, since DFA requires long data sets. The short-range (α_s, $4 \leq n \leq 16$) and long-range (α_l, $n > 16$) correlations were computed for each patient.

4) Wigner-Ville Distribution

Spectral analysis has been widely applied to separate the oscillatory components of the HRV relating to the sympathetic and parasympathetic response of the ANS [7], [22]. However, the spectrum does not tell us the time dependence of the frequency components. The time dependence of the frequency content is obscured, since the Fourier transform decomposes the signal into complex exponentials that are unlocalized in time. Furthermore,

spectral analysis of HRV requires some level of stationarity, which is a premise that is unlikely to hold.

The Wigner-Ville transform (WVT) [23] provides a spectral profile for each point of the time series, and therefore has the advantage of tracking the instantaneous changes in frequency and amplitude of each spectral component. From each spectrum, we obtained the power by integration of the profile of the spectrum in two relevant frequency bands: low frequency (LF) from 0.05 Hz to 0.15 Hz; high frequency (HF), from 0.15 Hz to 0.4 Hz [24]. To allow the spectral components to be compared in relative terms, the power in these two frequency bands were normalized by dividing by the total power. The instant values of LF/HF were calculated.

III. Results

The various measures for a representative OSAS patient are plotted in Fig. 1. Since the results for ApEn and SampEn were similar, only the latter is shown.

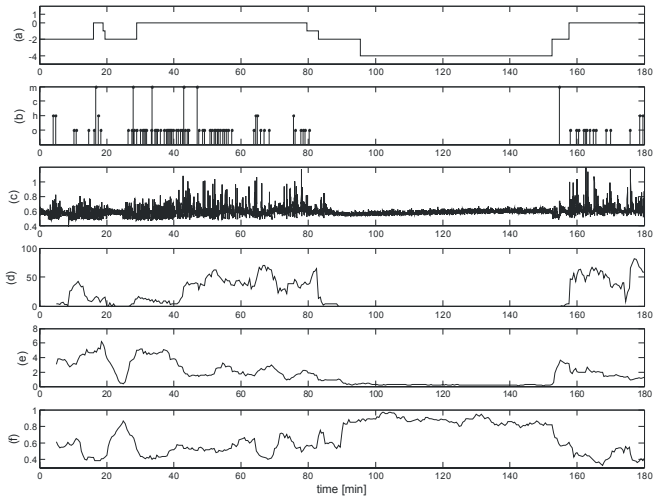

Fig. 1. Plots of various statistics, (a) Sleep stages (1 = wake, 0 = REM, -2 = stage 2, -4 = stage 4), (b) apnea/hypopnea events (1 = obstructive, 2 = hypopnea, 3 = central, 4 = mixed), (c) R-R interval, (d) noise limit %, (e) LF/HF ratio, (f) sample entropy

We compared the different measures in REM and NREM within each patient group. Statistical comparison between means was done using the Student's t-test. P-values less than 0.05 were considered statistically significant. The results of this comparison are shown in Table I.

TABLE I
In-Group Comparisons

Group	NL	SampEn	LF/HF
Severe	S	-	-
Mild	S	-	S
Normal	S	S	S

S = statistically significant between REM and NREM sleep

Next, we compared the various measures across patient groups, showing the discriminatory power of the different statistics. The result of this comparison is shown in Table II.

Finally, using the time-series metrics and the LF/HF power ratio as test statistics, the receiver operating characteristic (ROC) curves for distinguishing OSAS and normal subjects were calculated. The area under the ROC curve (AUC) was used to assess test performances. Sensitivity and specificity at the optimal threshold were calculated and are shown in Table III.

TABLE II
Cross-Group Comparisons

Groups		NL	SampEn	LF/HF	α_1
Severe vs. Normal	REM	S	-	S	-
	NREM	S	-	S	-
	Overall	S	-	S	S
Severe vs. Mild	REM	-	-	S	-
	NREM	-	S	S	-
	Overall	-	-	S	S
Mild vs. Normal	REM	S	-	-	-
	NREM	S	-	-	-
	Overall	S	-	-	-

S = statistically significant between sleep apnea severity groups

TABLE III
Classification Performance

Measures	AUC	Sensitivity	Specificity
NL	0.802	81.3%	72.2%
LF/HF	0.726	68.7%	77.8%
SampEn	0.649	75%	61.1%

IV. Discussion

An important contribution of this work is our finding that the numerical titration is more sensitive at identifying OSAS than other time-series metrics and even power-spectral parameters, as indicated by the AUCs (see Table III). This suggests that insofar as nonlinearity is an important mechanism underlying HRV, measurements which specifically characterize the nonlinearity of HRV may provide more direct and sensitive methods for assessing the physiological state. Noise limit (NL) has significant diagnostic value that may complement traditional spectral analysis of HRV.

On average, HRV exhibits higher chaotic intensity in REM compared to NREM sleep in children regardless of OSAS severity (see Table I), since apnea events occur predominantly during REM sleep. Noise limit was significantly increased during apnea episodes. This implies that the HRV has a low-dimensional chaotic characteristic, and the degree of chaos was pronouncedly enhanced with apnea episodes compared to stable breathing. This result is consistent with our previous findings [25]. In addition, Table I shows that the entropy statistics and the LF/HF ratio are less successful in discriminating between REM and NREM sleep in OSAS patient groups.

It is noteworthy that the HRV of the mildly apneic subjects mimics that of the severe OSAS patients in terms of the nonlinear dynamics; that is, the average chaos intensity, as measured by NL, for the mild OSAS group is comparable to that of the severe group. This observation makes NL suitable for the detection of OSAS, since we can use it to identify normal subjects from even the mild OSAS patients. However, the numerical-titration technique becomes less effective in classifying the severity of apnea.

With the Wigner-Ville transform, the LF/HF ratio represents the instantaneous relationship between sympathetic and parasympathetic modulation. When comparing our results with previous studies on spectral analysis of HRV during apnea, we can confirm several aspects with our results. In particular, there is a significant rise in the LF/HF ratio accompanying sleep apnea, reflecting sympathetic stimulation and reduction in parasympathetic activity elicited by apnea. This finding is consistent with previous studies.

Approximate entropy and sample entropy measure the unpredictability of fluctuations in HRV. Apneic patients showed slightly higher ApEn and SampEn which were interpreted as a decreased regularity of cardiac rhythm. The physiological mechanism underlying enhanced variability is not known, but seems likely to represent dysfunction of the ANS. In our pediatric data set, the noise is very high; therefore the validity of ApEn and SampEn calculations may be seriously compromised. Since the RRI time series is also non-stationary, little can be inferred from moment statistics and entropy calculations.

In this work, we have calculated the short- and long-range correlations (α_s and α_l) using DFA. The short range correlation is larger than the long-range correlation for all subjects. Severe OSAS subjects have lower short time scaling exponent ($p < 0.05$), and higher long range correlations ($p < 0.02$) than normal subjects. For many patients, the power law is observed to have more than two variations with segment length, suggesting that there may be more information in the power-law behavior that was overlooked by simply estimating the linear slopes over two predefined regions.

V. Conclusion

We have shown that HRV can be used as a reliable indicator of sleep states and as a screening test for pediatric sleep apnea. Certain methods of nonlinear dynamics might elicit valuable information for physiological interpretation of HRV. Since the HRV becomes more chaotic with apnea events, cardiac chaos can have diagnostic/prognostic values in OSAS screening.

Some statistics, such as approximate and sample entropy, may be too insensitive to detect the nonlinear perturbations of R-R interval in pediatric data, or too sensitive to noise, or both. More encouraging results have been obtained using numerical titration. The robustness of this method to noise exhibits tremendous potentials. We conjecture that application of nonlinear techniques in conjunction with spectral analysis of HRV would provide greater diagnostic accuracy.

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