PP and PR Interval Variations in Pediatric Subjects Being Evaluated for Obstructive Sleep Apnea

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Abstract

This work considers measures of RR, as a surrogate to the PP interval, and PR intervals in pediatric subjects with mild/severe obstructive sleep apnea, and control subjects. Analysis is carried out in a total of 50 subjects (ages 1-16 y, mean 8.7), of which 22 are control (AHI 0.06 +/-0.13), 17 are mild, and 11 are severe. A range of time domain features of RR and PR intervals were considered, with six measures showing statistical differences between control and apneic subjects. Spectral features (low frequency component of RR, and high frequency component of PR) also provided statistically significant differences between classes. Further time domain analysis was carried out by calculating the average RR and PR interval sequences in response to an obstructive event. The average RR sequence contained the well-known bradycardia/tachycardia swing. However, in most obstructive sleep apnea subjects (21 out of 28), the average PR sequence was out of phase with the RR pattern, indicative of a predominance of refractory effects in setting the AV conduction time in these subjects.

1. Introduction

Obstructive sleep apnea (OSA) is the most common form of sleep disordered breathing (SDB) seen in children, characterized by prolonged partial or complete obstruction of the upper airway. These obstructive events lead to oxygen desaturation, and also cause fragmentation and disruption in sleeping patterns. The prevalence of OSA among children is believed to be in the range of 2-3%, with prevalence as high as 10 to 20% in habitually snoring children [1]. Unlike adults with OSA, who are typically male, overweight and frequently wake up at night, OSA in children is more difficult to recognize and diagnose, and has a similar prevalence in both boys and girls. This can result in under diagnosis of OSA in children, the consequences of which can include behavioral problems, failure to thrive, attention deficit disorder, enuresis, cor-pulmonale and congestive heart failure [2-6].

It is well established that obstructive apneas and hypopneas influence changes in heart rate. Obstructive apneas are usually associated with a mild bradycardia during the apneic event followed by a tachycardia after the apneic event. These cyclic variations in autonomic drive to the heart were first reported in adults by Guilleminault *et al.* [7] and have been used to identify episodes of obstructive apneas in adults [8]. These variations have also been observed in children [9]. In this study we wish to analyze these cyclic variations in heart rate, and to assess the efficiency of simple HRV measures in assessment of pediatric OSA.

In addition, we wish to assess the influence of OSA events on intra-cardiac timing, specifically, its influence on atrio-ventricular (AV) conduction time. The autonomic nervous system modulates neural activity at both the sino-atrial (SA) and at the atrio-ventricular (AV) node with parasympathetic activation decreasing firing at the SA node and the conduction velocity through the AV node while sympathetic activity increases the firing rate and the conduction velocity. In this regard, it is reasonable to expect that cyclic variations seen in heart variations during apneic events may also be present in the form of cyclic variations in AV conduction time. In practice, however, the influence of autonomic activity at the AV node is further complicated by intrinsic nodal effects such as refractoriness, facilitation and fatigue [10]. Refractoriness, which is often the most significant intrinsic effect on AV conduction, can lead to paradoxical lengthening of the AV interval in response to shorter RR intervals. Analysis of the cyclic variations in heart rate and AV conduction time are assessed using the RR (as surrogate to PP) and PR interval measurements obtained from the surface electrocardiogram (ECG). In this paper, we report on the relative influence of refractory and autonomic effects on the AV conduction time in response to obstructive events. We also considered whether time and frequency domain measures derived from the PR interval could also be used to distinguish between normal, mild and severe OSA pediatric subjects. Although the significance and characterization of event counts such as the AHI index is less clear for pediatric OSA, for the purpose of this paper, we consider normal subjects to

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have AHI<1, mild OSA is defined as 1≤AHI≤15 and moderate/severe OSA as AHI>15.

2. Methods

Children referred for OSA evaluation underwent a standard polysomnographic study at the Sleep Medicine Center of Kosair Children's Hospital, Louisville, with ethics approval and parental consent. Children were studied for up to 12 hours in a quiet, darkened room, ambient temp 24^{o}C in the company of one of their parents. Lights out was between 21:00 and 21:30hrs; subjects were woken at 07:00 hrs. No drugs were used to induce sleep. Measurements included chest and abdominal wall movement by respiratory impedance or inductance plethysmography, heart rate by lead I ECG at 256 Hz and air flow with a sidestream end-tidal capnograph which also provided breath-by-breath assessment of end-tidal carbon dioxide levels and/or a thermistor. Arterial oxygen saturation (SpO2) was assessed by pulse oximetry with simultaneous recording of the pulse waveform. The bilateral electro-oculogram, 8 EEG channels, chin and anterior tibial electromyograms, and analog output from a body position sensor were also monitored. Digital signal acquisition was performed using a commercial polysomnography system (Medcare, Buffalo, NY).

Obstructive apnea (OA) was defined as the absence of airflow with continued chest wall and abdominal movement for at least two breaths. Obstructive hypopneas (OH) were defined as a 50% or more decrease in nasal flow with a corresponding decrease of 4% or more in SpO2 and/or arousal and were scored if the duration was at least two breaths. The apnea/hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time (TST).

3. ECG signal analysis

The 256 Hz ECG was interpolated to 1 KHz using cubic spline interpolation and the QRS peaks were extracted using a Hilbert Transform based detector. The P peaks were extracted using a combination of a search back and template matching algorithm. The RR interval was used as a surrogate to the PP interval and the PR interval was defined as the measurement from the current P peak to the following QRS peak. PR is used as a surrogate for AV conduction time.

The standard time domain techniques used to analyze the RR interval variations included mean RR, SDNN, SDANN, RMSSD and pNN50, which are outlined in [11]. Since ectopic beats were rare in all subjects, we used RR intervals in place of NN intervals. Statistical measures of the PR intervals include mean PR, SDPR (standard deviation of the PR interval), SDAPR (standard deviation of 5 minute PR means), RMSSDPR (square root of the mean squared differences of successive PR intervals), and pPR10 (the proportion of PR intervals which differ by more than 10 ms from the preceding PR interval). Frequency domain techniques include spectral analysis of the interval tachograms over the sleeping period using the Burg's parametric spectral density estimation (of order 13) over the whole sleeping period. The spectral results for the LF and HF components are expressed as a percentage of the total power spectral density**.**

As a further analysis, we calculated the "average" RR and PR interval sequences in response to obstructive apneas. We define an "average" response by taking sets of 100 RR and PR intervals centered about the time of onset of an obstructive apnea event (as determined by the human scorer). A typical subject might have tens or even hundreds of obstructive events per night, and by averaging together the RR and PR sequences, one obtains the "average" autonomic response.

4. Results

Table 1 summarizes the time-domain measures for the fifty datasets (22 normal, 17 with mild OSA, and 11 with severe OSA). Statistically significant differences between the groups were assessed using analysis of variance (ANOVA). Of the time domain features, mean RR, NN50, pNN50, PR10, pPR10 and RMSSDPR appear to provide the most discrimination across classes. Table 1 also gives the values of the spectral features calculated for each of the three classes. The results in Table 1 indicate that spectral features do differ in control subjects and those with mild and severe apneas. In particular, a high AHI index is associated with higher values in the LF component of the RR interval spectra. In contrast, a high AHI is associated with higher values in both the LF and HF component in the PR interval spectra. The higher LF component in the RR interval may be explained by higher sympathetic activation during apneas or reduced parasympathetic activation resulting from possible attenuated RSA during oxygen desaturation with obstructive events [12]. The lower LF/HF ratio in the PR interval variations may be a result of the dynamic properties of the AV node or insignificant attenuation of the respiratory influence on the AV node. Indeed as mentioned in [13] although respiration does modulate the variation in the PR interval its role may not be as significant as RSA on heart rate. Figure 1 shows the "average" RR and PR sequence in response to obstructive events, in a subject with an AHI of 14.9, using the interval averaging technique described above. In this case, the average sequence was obtained by combining 98 100-beat sequences over the night's recordings. It clearly shows that the apnea is associated with a bradycardia (typically lasting 10 beats) followed by a recovery

tachycardia of similar duration.

Measures	Subjects *Control*	*Mild*	*Severe*	*ANOVA* *p*
Age (yrs)	9.10 ± 3.33	8.86 ± 4.54	8.01 ± 5.38	0.7834
Mean RR (ms)	795.90 ±97.94	673.52 ±90.95	669.13 ± 104.18	0.0002*
SDNN (ms)	108.06 ± 32.98	95.13 ± 47.88	91.56 ± 28.70	0.4106
SDANN (ms)	79.81 ± 44.57	63.79 ± 44.32	63.50 ± 38.17	0.4301
RMSSD (ms)	85.58 ± 43.05	66.28 ± 56.26	65.46 ± 30.16	0.3315
NN50	14339.77 ± 7059.05	9380.64 ± 6941.61	9484.72 ± 5416.27	0.0449*
pNN50 (%)	0.38 ± 0.20	0.23 ± 0.19	0.23 ± 0.16	0.0292*
Mean PR (ms)	122.65 ± 10.27	125.18 ± 13.23	131.46 ± 11.52	0.1323
SDPR (ms)	8.17 ± 3.93	6.79 ± 2.64	10.57 ± 5.73	0.0634
SDAPR (ms)	7.03 ± 5.22	6.28 ± 3.32	7.57 ± 4.47	0.9336
RMSSDPR (ms)	7.16 ± 4.55	5.52 ± 1.94	10.99 ± 7.78	0.0188*
PR10	3701.54 ± 3843.50	3428.76 ± 2188.47	7929.54 ± 6660.38	0.0149*
pPR10 (%)	0.09 ± 0.09	0.07 ± 0.04	0.174 ± 0.13	0.0293*
LF (RR) (%)	15.22 ± 4.04	12.88 ± 5.63	19.39 ± 9.70	0.0315*
HF (RR) (%)	22.65 ± 13.05	17.89 ± 12.36	18.35 ± 9.37	0.4181
LF/HF (RR)	0.87 ± 0.47	1.11± 0.83	1.32 ± 0.97	0.2334
LF (PR) (%)	12.43 ± 4.74	12.78 ± 6.59	17.24 ± 7.11	0.0823
HF (PR) (%)	23.09 ± 12.29	22.42 ± 9.72	34.28 ± 16.67	0.0358*
LF/HF (PR)	0.66± 0.34	0.65 ± 0.47	0.63 ± 0.52	0.9732

Table 1: Time and frequency domain measures [Mean ± SD] *p < 0.05

The overall magnitude of the variation is about ±40 ms (corresponding to approximately ±6bpm). Interestingly there is evidence of a secondary bradycardia/tachycardia effect. However, the average PR sequence follows a quite different temporal path; it shortens in response to the bradycardia, and lengthens during the tachycardia. The overall magnitude of the variation is ±3 ms. An interpretation of this is that the AV conduction time in this subject is dominated by refractory effects. However, this is not always the case. In Figure 2, we show "average" RR and PR sequences from a subject with an AHI of 13.5 and 104 100-beat sequences. In this case, RR and PR intervals are in phase, indicating that autonomic effects are the main determinant in setting the AV conduction time. However, it would appear that in pediatric subjects, the majority is refractory dominated. Of the 28 subjects who suffered from OSA, 21 exhibit opposite changes in RR and PR interval lengths.

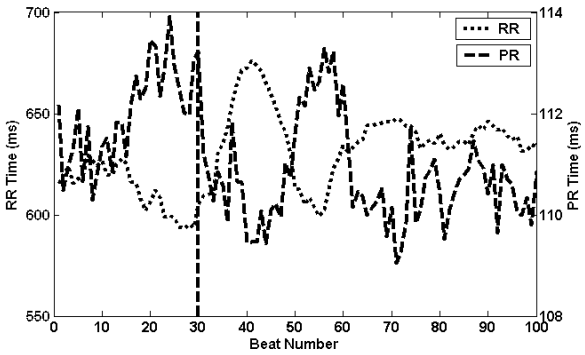

Figure 1. Refractory effects during apnea.

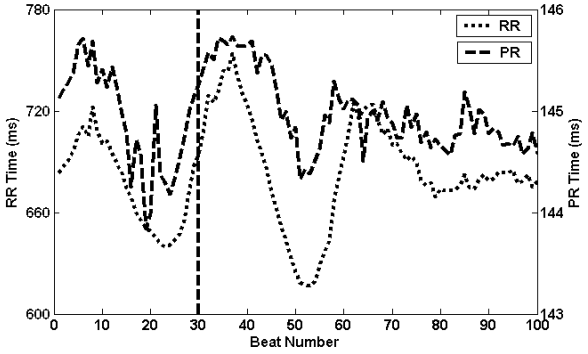

Figure 2. Autonomic linkages during apnea.

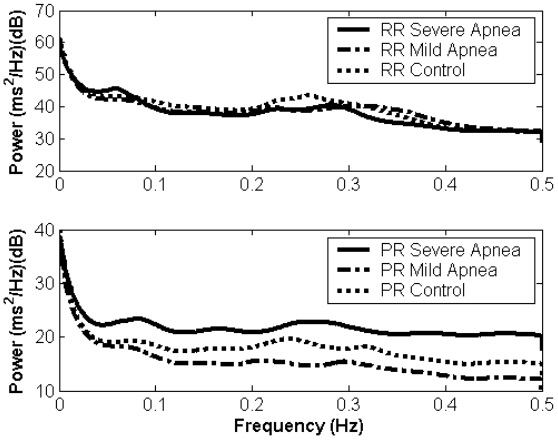

Figure 3. Power Spectral Density estimations of control subjects and those with mild and severe apnea.

5. Discussion and conclusions

This study investigated the relationship between heart rate variation and atrial conduction times in pediatric subjects with and without obstructive sleep apnea. Limitations to the work which should be considered include quantization error in estimating a relatively short signal such as the PR interval, possible misdetections of biphasic P peaks - these however were rare in the data segments under consideration. Mechanical effects on the heart during apnea were not considered.

Variations in heart rate and AV conduction times were non-invasively assessed using the RR interval, as a surrogate to the PP interval, and the PR interval of the ECG. Subjects were placed into one of three groups based on their AHI index. Time and frequency domain measures were employed to analyze possible differences between control, mild and severe OSA pediatric subjects Time domain analysis of the datasets indicated that subjects with both mild and severe OSA had a significantly lower mean RR than control subjects. This may be due to either increased sympathetic or reduced parasympathetic activity in subjects with obstructive apneas and hypopneas. Time domain measures such as pNN50 also showed significant differences between the RR intervals of apnea and control subjects with the control group showing a much higher percentage. These results contrast with the higher mean PR and pPR10 percentage for PR intervals in subjects with severe OSA, which is further verified by the spectral results seen in Table 2 and Figure 3. This contrasting behavior may be a result of the complex dynamic behavior of the atrio-ventricular node. Indeed refractory effects seem to play a central role in determining AV conduction times during obstructive apneas with 21 of the 28 OSA subjects exhibiting opposite changes in RR and PR interval lengths. Spectral analysis of the datasets showed strong LF and respiratory HF components of the PR interval with subjects with a higher AHI index demonstrating more pronounced fluctuations in the PR intervals of subjects with moderate to severe OSA.

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References

[1] Young T, Peppard PE, Gottlieb DJ. Epidemiology of Obstructive Sleep Apnea, A Population Health Perspective. Am J Respir Crit Care Med. 2002 May 1;165(9):1217-39.

[2] Gottlieb DJ, Vezina RM, Chase C, Lesko SM, Heeren TC, Weese-Mayer DE, Auerbach SH, Corwin MJ. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. Pediatrics. 2003 Oct;112(4):870-7.

[3] Chervin RD, Archbold KH, Dillon JE, Panahi P, Pituch KJ, Dahl RE, Guilleminault C. Inattention, hyperactivity, and symptoms of sleep-disordered breathing. Pediatrics. 2002 Mar;109(3):449-56.

[4] Owens J, Opipari L, Nobile C, Spirito A. Sleep and daytime behavior in children with obstructive sleep apnea and behavioral sleep disorders. Pediatrics. 1998 Nov; 102(5) :1178 - 84.

[5] O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Smith NH, McNally N, McClimment MC, Gozal D. Neurobehavioral correlates of sleep-disordered breathing in children. J Sleep Res. 2004 Jun; 13(2):165-72.

[6] American Thoracic Society. Cardiorespiratory sleep studies in children. Establishment of normative data and polysomnographic predictors of morbidity. American Thoracic Society. Am J Respir Crit Care Med. 1999 Oct;160(4):1381-7.

[7] Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A. Cyclical variation of the heart rate in sleep apnoea syndrome. Mechanisms, and usefulness of 24 h electrocardiography as a screening technique. Lancet. 1984 Jan 21; 1(8369): 126-31.

[8] Stein PK, Duntley SP, Domitrovich PP, Nishith P, Carney RM. A simple method to identify sleep apnea using Holter recordings. J Cardiovasc Electrophysiol, 2003 May, 14(5): 467-73.

[9] Aljadeff G, Gozal D, Schechtman VL, Burrell B, Harper RM, Ward SL. Heart rate variability in children with obstructive sleep apnea. Sleep. 1997 Feb; 20(2): 151-7.

[10] Billette J, Nattel S. Dynamic behavior of the atrioventricular node: a functional model of interaction between recovery, facilitation, and fatigue. J Cardiovasc Electrophysiol. 1994 Jan;5(1):90-102.

[11] American Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiolgy. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996 Mar 1; 93 (5): 1043-1065.

[12] Yasuma F, Hayano J. Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? Chest. 2004 Feb; 125(2): 683-90.

[13] Shouldice R, Heneghan C, Nolan P. Methods of Quantifying Respiratory Modulation in Human PR Electrocardiographic Intervals. Proc 24th Annual IEEE International Conference on Engineering in Medicine and Biology (EMBS-BMES), October 2002.

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