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Original Article

Nocturnal autonomic function in preschool children with sleep-disordered breathing

Lauren C. Nisbet [a], Stephanie R. Yiallourou [a], Gillian M. Nixon [a,b], Sarah N. Biggs [a], Margot J. Davey [a,b], John Trinder [c], Lisa M. Walter [a,1], Rosemary S.C. Horne [a,*,1]

[a] The Ritchie Centre, Monash Institute of Medical Research, Monash University, Melbourne, Australia
[b] Melbourne Children's Sleep Centre, Monash Children's, Monash Medical Centre, Melbourne, Australia
[c] Discipline of Psychological Sciences, University of Melbourne, Melbourne, Australia

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is associated with autonomic dysfunction in adults and school-aged children; however, this association has not been investigated in preschool children. We aimed to analyze heart rate variability (HRV) and catecholamine levels in preschool children with OSA.
Methods: One hundred and forty-two snoring children aged 3–5 years and 38 nonsnoring control group children underwent overnight polysomnography (PSG). Nocturnal urinary catecholamines were measured in 120 children. Children were grouped according to their obstructive apnea–hypopnea index (OAHI) (control [no snoring], OAHI $\leqslant$ 1 event/h; primary snoring, OAHI $\leqslant$ 1 event/h; mild OSA OAHI > 1 $\leqslant$ 5 events/h; moderate to severe [MS] OSA, OAHI > 5 events/h). The HRV parameters for each child were averaged during rapid eye movement (REM) and non-REM (NREM) sleep.
Results: During stable sleep, low-frequency (LF) HRV was similar between groups. High-frequency (HF) HRV was higher in the MS OSA group compared with the control group during all sleep stages (NREM sleep stages 1 and 2 [NREM1/2], 4234 ± 523 ms^2 vs 2604 ± 457 ms^2; NREM sleep stages 3 and 4 [NREM3/4], 4152 ± 741 ms^2 vs 3035 ± 647 ms^2; REM, 1836 ± 255 ms^2 vs 1456 ± 292 ms^2; $P < .01$ for all). The LF/HF ratio was lower in the MS OSA group compared with the control group (NREM1/2, 0.4 ± 0.06 vs 0.7 ± 0.05; NREM3/4, 0.3 ± 0.06 vs 0.4 ± 0.05; REM, 0.8 ± 0.1 vs 1.3 ± 0.1; $P < .01$ for all). Catecholamine levels were not different between groups.
Conclusions: In preschool children, OSA is associated with altered HRV, largely due to the HF fluctuations in heart rate (HR) which occur during respiratory events and are still evident during stable sleep. The preschool age may represent a window of opportunity for treatment of OSA before the onset of the severe autonomic dysfunction associated with OSA in adults and older children.

1. Introduction

Obstructive sleep apnea (OSA) in adults is associated with cardiovascular morbidity and mortality [1,2]. OSA affects 1% to 4% of children [3] and is characterized by recurrent airway collapse resulting in intermittent hypoxia and hypercapnia, intrathoracic pressure swings, arousals, and sleep disruption. The hallmark symptom of OSA is snoring, and habitual snoring (>3 times/week) occurs in 3% to 15% of children [3]. Snoring without gas exchange abnormalities or sleep fragmentation is termed *primary snoring* (PS), which together with OSA forms a spectrum of disorders commonly referred to as sleep-disordered breathing (SDB). In school-aged children, the cardiovascular repercussions of SDB include elevated blood pressure (BP) [4–8], decreased nocturnal baroreflex gain [9], and left ventricular dysfunction [10,11].

Autonomic dysfunction is thought to play a key role in the development of the cardiac consequences of both adult and pediatric SDB [12–14]. Obstructive events elicit significant changes in heart rate (HR) and BP [15–17], notably an acute tachycardia and surge in sympathetic activity at respiratory event termination; the latter has been measured by microelectrode insertion directly in adults [16,18]. Heart rate variability (HRV) is an alternative noninvasive method for assessment of autonomic control. Fluctuations in HR, controlled by the opposing parasympathetic and sympathetic nervous systems, can be measured by both time- and frequency-domain methods. The latter method separates high-frequency power (HF), reflecting parasympathetic activity through respiratory related changes (sinus arrhythmia), and low-frequency

* Corresponding author. Address: The Ritchie Centre, Level 5, Monash Medical Centre, 246 Clayton Rd, Clayton, Victoria 3168, Australia. Tel.: +61 3 9594 5100; fax: +61 3 9594 6811.
E-mail address: rosemary.horne@monash.edu (R.S.C. Horne).
[1] Denotes co-senior-authorship.

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power (LF), reflecting both sympathetic and parasympathetic activity as mediated by the baroreflex [19,20]. OSA in adults has been associated with reduced HRV [18,21,22], and the few studies of HRV in school-aged children with OSA have similarly indicated autonomic dysfunction [23–27]. Another noninvasive marker of autonomic activity is urinary catecholamine concentration, which is representative of generalized sympathetic activity. Recent studies in children have shown that urinary adrenaline, noradrenaline, and dopamine levels are significantly correlated with the apnea-hypopnea index [28–30].

The prevalence of snoring peaks in the preschool years [31]. To date, there have been no studies investigating the effects of SDB on autonomic cardiovascular control in a purely preschool-aged cohort. We aimed to study SDB severity and sleep-related alterations in HRV in preschool children and correlate levels of urinary catecholamines with indices of HRV to provide a more complete understanding of autonomic function. Based on findings in older children, we hypothesized that preschool children with SDB would have decreased HRV parameters (LF, HF, and total power) and increased urinary catecholamines when compared to the nonsnoring control group.

2. Methods

Our study formed part of a larger study investigating the neurocognitive and cardiovascular effects of SDB in preschool children. Neurobehavioral [32], homeostatic regulation [33], sleep disturbance data [34], and overnight changes in BP [35] have been previously published. The Southern Health and Monash University Human Research Ethics Committees approved the protocol. Written informed consent was obtained from parents after a full explanation of the procedure. Recruitment protocol and polysomnography (PSG) methods have been previously reported [32–35]. In summary, we recruited 192 preschool children (aged, 3–5 y); the sample comprised 151 children from the community who were clinically referred and 41 children who had no history of snoring.

Children with conditions or taking medications known to affect sleep, breathing, BP, or neurocognitive function were not recruited. All children were otherwise healthy and underwent routine pediatric PSG. Sleep staging and scoring were performed in accordance with international standards at the time of study [36–39]. The obstructive apnea–hypopnea index (OAHI) was used to define severity groups (PS, OAHI $\leqslant$ 1 event/h; mild OSA, OAHI > 1–$\leqslant$ 5 events/h; and moderate to severe [MS] OSA, OAHI > 5 events/h). The control group had an OAHI $\leqslant$ 1 event per hour and did not snore. PSG recording included wake before sleep onset for a minimum of 10 min. On the night of the PSG study, a 12-hour urine sample was collected (7:00 pm–7:00 am) via bottle or nappy, as previously described [28]. Urinary catecholamines, including dopamine, noradrenaline, and adrenaline, were measured using high performance liquid chromatography, with adjustment for renal function using creatinine concentration [28–30,40].

Electrocardiogram (ECG) was sampled at 512 Hz. Two-minute artifact-free bins of the same sleep stage were analyzed across the overnight recording [26]. Wake after sleep onset was not included. The HRV analysis was performed in LabChart (7.2, ADInstruments, Australia) using normal-to-normal intervals (NN) in both the time and frequency domain. The time domain comprised the mean NN (inverse to HR), the SDNN (standard deviation of the NN interval), and the RMSSD (square root of the mean squared differences in successive NN intervals). The frequency domain comprised the power spectral density determined LF (0.04–0.15 Hz), HF (0.15–0.4 Hz), and total power ($\leqslant$0.4 Hz), and the LF/HF was calculated as a measure of sympathovagal balance [20].

The HRV indices for each child were averaged for the whole sleep period then separated into wake before sleep onset, rapid eye movement (REM) sleep, non-REM (NREM) sleep stages 1 and 2 (NREM1/2), and NREM sleep stages 3 and 4 (NREM3/4). Subsequent analysis of 2-minute bins containing respiratory events, arousals, or movements were excluded to investigate stable sleep in the control and MS OSA groups, thereby excluding the acute effects associated with respiratory events. Because the MS OSA group had the most respiratory events, this group was chosen to best demonstrate the effects of stable sleep.

Statistical analyses were performed using SPSS® (IBM® Statistics, version 19). The HRV and catecholamine data were natural log transformed. Demographic, PSG, and catecholamine data were compared between groups using one-way analysis of variance (ANOVA) with Student–Newman–Keuls post hoc testing and Kruskal–Wallis ANOVA on ranks, with Mann–Whitney *U* test when the data were not normally distributed. No correlation was found between HRV and BMI *z* score using Pearson product moment correlations coefficients. The HRV indices were assessed using 2-way general linear model repeated measures covarying for sleep period HR [26] with post hoc testing when appropriate (multivariate analysis, $P < .05$), using one-way ANOVA and one-way repeated measures ANOVA in each stage and group, respectively, to identify differences. Spearman rank correlations assessed the relationship between catecholamines and OAHI. Simple linear regression determined if HRV parameters were predictive of catecholamine levels. Data are presented as mean (standard error) or median (range), with significance taken at $P < .05$.

3. Results

Of the 192 children studied, 12 children were excluded because the ECG artifact precluded analysis. The HRV in 180 children (control, 38; PS, 74; mild OSA, 39; MS OSA, 29) and urinary catecholamines in 120 of these children (control, 28; PS, 49; mild OSA, 25; MS OSA, 18) are reported below. The HRV findings in the time and frequency domains were similar. Time-domain HRV results are reported in the Supplemental Material. Results of frequency-domain HRV analyses are presented below.

3.1. Demographic and PSG characteristics

As presented in Table 1, groups did not differ in age, sex, or average sleep period HR. The mild OSA group had a higher BMI *z* score than the control group ($P < .05$). Due to study design, the OAHI was higher and oxygen saturation nadir was lower in the MS OSA group compared to other groups ($P < .01$ for all).

3.2. Effect of SDB severity on HRV

Fig. 1 compares frequency-domain HRV parameters between the groups during each wake-sleep stage. LF was higher in the MS OSA group compared to the PS and mild OSA groups during wake, compared to all groups during NREM1/2, and compared to control and mild OSA groups during REM sleep ($P < .05$ for all). HF was higher in the MS OSA group compared to the PS group during wake, compared to the control and PS groups during NREM1/2, and compared to the control group during REM sleep ($P < .01$ for all). Total power was higher in the MS OSA group compared to the PS group during wake, compared to all groups during NREM1/2, and compared to the control group during REM sleep ($P < .05$ for all). There were no group differences in LF, HF, or total power during NREM3/4 sleep. The LF/HF ratio differed between groups during wake ($P < .05$), though targeted differences did not meet significance with post hoc testing. The LF/HF ratio was lower