Acute Cardiovascular Changes with Obstructive Events in Children with Sleep Disordered Breathing

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Study Objectives: Obstructive apneas in adults are associated with acute changes in blood pressure (BP) and heart rate (HR) that may contribute to poor cardiovascular outcome. Children with sleep disordered breathing (SDB) are similarly at risk for cardiovascular complications. We aimed to test the hypothesis that BP and HR are augmented during obstructive events in children equivalent to levels reported in adults.

Design: Beat-by-beat mean arterial pressure (MAP) and HR were analyzed over the course of obstructive events (pre, early, late, and post-event) during NREM and REM sleep and compared using 2-way ANOVA with post hoc analyses.

Setting: Pediatric sleep laboratory.

Patients or Participants: 30 children (15M/15F) aged 7–12 y referred for investigation of SDB

Interventions: N/A

Measurements and Results: All children underwent overnight polysomnography with continuous BP recording. MAP and HR increased significantly from late to post event in both sleep states (mean ± SEM, NREM: MAP, 74 ± 3 to 93 ± 3 mm Hg; HR, 76 ± 2 to 97 ± 2 bpm. REM: MAP, 76 ± 3 to 89 ± 3 mm Hg; HR, 76 ± 2 to 91 ± 2 bpm. $P < 0.05$ for all). NREM sleep state and arousal from sleep were significant independent predictors of the magnitude of cardiovascular change from late to post event ($P < 0.05$ for all).

Conclusions: Children with SDB experience significant changes in HR and BP during obstructive events with magnitudes that are similar to levels reported in adults. These changes are more pronounced during NREM sleep and with arousal. These acute cardiovascular changes may have important implications for poor cardiovascular outcome in children with OSA as repetitive cardiovascular perturbations may contribute to the development of hypertension.

Keywords: Pediatric, sleep, apnea, blood pressure, heart rate

Citation: O'Driscoll DM; Foster AM; Ng ML; Yang JSC; Bashir F; Nixon GM; Davey MJ; Anderson V; Walker AM; Trinder J; Horne RSC. Acute cardiovascular changes with obstructive events in children with sleep disordered breathing. *SLEEP* 2009;32(10):1265-1271.

OBSTRUCTIVE SLEEP APNEA (OSA) IN ADULTS IS ASSOCIATED WITH CENTRAL OBESITY,[1] WHILE IN CHILDREN AIRWAY OBSTRUCTION IS PREDOMINANTLY attributable to adenotonsillar hypertrophy.[2] Although different in pathophysiology, the prevalence of OSA in adults and children is similar at 2% to 4%[3] and 1% to 3%,[4] respectively. The association between adult OSA and cardiovascular complications is well described.[5] Likewise there is now emerging evidence that children with OSA are similarly affected, with increasing reports citing an association between pediatric OSA and the development of hypertension, increased blood pressure (BP) variability and decreased nocturnal BP dipping.[6-8] Although a meta-analysis of pediatric studies published before 2007, found no evidence that OSA in childhood increases the risk of elevated BP,[9] recent large population-based studies have shown that BP is strongly associated with OSA,[10] and this association is independent of obesity.[11] OSA has also been shown to be associated with increased sympathetic nervous system activity as measured by pulse arterial tonometry during autonomic challenges,[12] and by increased levels of urinary[13] and plasma norepinephrine.[14] Interestingly, OSA in children has also been shown to be associated with endothelial dysfunction, which was reversed after treatment with adenotonsillectomy.[15]

In adult patients with OSA, a number of factors have been implicated in the development of hypertension, including resetting of baroreceptors, endothelial dysfunction, and the repetitive surges in cardiovascular activity that occur during an obstructive apnea or hypopnea.[5] In adults, it has been demonstrated that both heart rate (HR) and BP initially decrease and then progressively increase during an obstructive event following occlusion of the upper airway.[16,17] Peripheral sympathetic activity increases during the obstructive event,[18] most likely caused by the synergistic influence of hypoxia and hypercapnia. Upon resumption of ventilation, and coincident with arousal from sleep, there is a large surge in cardiovascular activity—tachycardia and an increase in cardiac output[19] superimposed upon hypoxia-induced peripheral vasoconstriction,[16] resulting in a large increase in BP. Cardiovascular analyses during and post obstructive events in adults have reported acute increases in mean BP and HR of approximately 20 mm Hg[20,21] and 15 bpm,[17,20,22] respectively.

In children with OSA, overall nocturnal pulse rate and pulse rate variability have been shown to decrease after adenotonsillectomy.[23] However, to date, the acute cardiovascular changes over the course of an obstructive event have not been explored in children. Despite the differing pathophysiology of OSA be-

Submitted for publication January, 2009
Submitted in final revised form April, 2009
Accepted for publication May, 2009
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tween adults and children, the link between the condition and hypertension appears common to both. We reasoned then, that children would have equivalent changes in cardiovascular activity during obstructive events to adults. Given the recent evidence for an association between vascular changes during childhood and adult cardiovascular disease,[24] cardiovascular perturbations of this magnitude may have significant long-term clinical implications. The aim of the present study was to determine the magnitude of BP and HR augmentation during an obstructive event in children with sleep disordered breathing (SDB) and to compare these values to values for adult OSA patients that have been reported in the literature. To achieve this, we measured beat-by-beat BP and HR over the course of obstructive events during sleep in children during both NREM and REM sleep.

METHODS

The Monash University and Southern Health Human Research Ethics Committees granted ethical approval for this project. Written informed consent was obtained from parents and verbal assent from the children prior to commencement of the study.

Subjects

Fifty children (28M/22F) referred for investigation of SDB took part in this study. All children were aged between 7–12 y and were otherwise healthy and on no medication, apart from 9 children diagnosed with asthma who were taking inhaled bronchodilators and/or inhaled steroid treatment.

Protocol

All children had office BP measured with a sphygmomanometer on the upper arm using standard techniques.[25] To account for the effects of age, gender, and height, systolic and diastolic measurements were converted to a z-score according to published criteria.[25] Height and weight were recorded, and body mass index (BMI) calculated. As with BP, BMI was converted to a z-score according to published criteria to account for the effects of age and gender.[26]

All children underwent routine overnight polysomnography (PSG) using a commercially available PSG system (Series S Sleep System, Compumedics, Melbourne, Australia). Electroencephalograms (EEG: C4/A1, O2/A1), electroculograms (EOG: left and right outer canthus), an electromyogram (EMG: submentalis muscle), electrocardiogram (ECG), left and right leg EMG and body position were recorded. Oxygen saturation (SpO_2) was measured by pulse oximetry (Biox 3700e, Ohmeda, Boulder, CO, USA) and thoracic and abdominal breathing movements recorded via uncalibrated respiratory inductance plethysmography (z-RIP belts, Pro-Tech Services Inc., Mukilteo, WA, USA). Both end-tidal and transcutaneous carbon dioxide ($PetCO_2$: Capnocheck Plus, BCI Inc., Waukesha, WI, USA; TCO_2: TCM3, Radiometer, Copenhagen, Denmark) were recorded, and airflow was measured via nasal pressure and oronasal thermistor (Compumedics, Melbourne, Australia). In addition to standard PSG recordings, continuous BP recordings were made using finger photoplethysmography (Finometer, Finapres Medical Systems, Arnhem, The Netherlands). BP measured via finger photoplethysmography was matched with the sphygmomanometer measurement during quiet wakefulness prior to sleep onset within ± 5mm Hg for both systolic and diastolic measurements. Following the PSG study, data were transferred via European data format to data analysis software (Chart 5, ADInstruments, Sydney, Australia) for detailed cardiovascular analysis.

Data Analysis

Sleep was scored in 30-s epochs according to standard criteria.[27] Arousals were scored as either subcortical activations (see below) or as by ASDA definition.[28] Subcortical activations were scored when ≥ 2 of the following events occurred and met criteria described by Mograss et al.[29]: an increase in EMG, an increase in HR, or a body movement (i.e., autonomic arousals not meeting ASDA criteria). Respiratory events were scored when ≥ 2 respiratory cycles in duration.[30] Obstructive apneas, mixed apneas, and hypopneas were defined according to standard criteria: obstructive apnea was defined as the cessation of airflow in the presence of respiratory effort; obstructive hypopnea was defined as ≥ 50% decrease in the amplitude of the airflow signal with paradoxical chest and abdominal movements and an associated arousal and/or fall ≥ 3% in oxygen saturation.[31]

An obstructive apnea hypopnea index (OAHI) was calculated, defined as the total number of obstructive apneas, mixed apneas, and obstructive hypopneas per hour of total sleep time. Diagnostic criteria for the classification of OSA severity followed current clinical practice: children were categorized as having primary snoring (PS, OAHI < 1 event/h); mild OSA (OAHI of 1–5 events/h); or moderate/severe OSA (OAHI > 5 events/h).

For cardiovascular analysis, only respiratory events ≥ 10 s in duration were examined in order to be comparable with adult data. Beat-by-beat BP and HR were analyzed and averaged for the following periods: *pre-event* (10 s immediately preceding the apnea/hypopnea), *early-event* (first half of apnea/hypopnea), *late-event* (last half of apnea/hypopnea), and *post-event* (average of the 3 consecutive peak measurements within 15 s of event termination) as illustrated in Figure 1. An advantage of this method was that cardiovascular data during events of different durations could be grouped and compared.[16]

Statistical Analysis

Statistical analysis was performed using Sigma Stat (Version 3.0, SPSS Inc., Chicago, IL, USA) and Intercooled Stata (Version 6, Stata Corp, Texas, USA). Demographic data and PSG variables were compared across SDB severity using 1-way ANOVA on ranks with Dunn's post hoc testing. For cardiovascular variables, within-subject values were averaged for each sleep state to ensure that each subject contributed once to the group mean. Sleep state by phase of events were assessed in 2-way ANOVAs with Student-Newman-Keuls post hoc analysis to assess the mean arterial BP (MAP) and HR changes across the obstructive event. The event type (apnea or hypopnea), and the SDB severity of the child were also assessed using 2-way ANOVAs but were dropped from the analysis due to lack of significance (see Results).

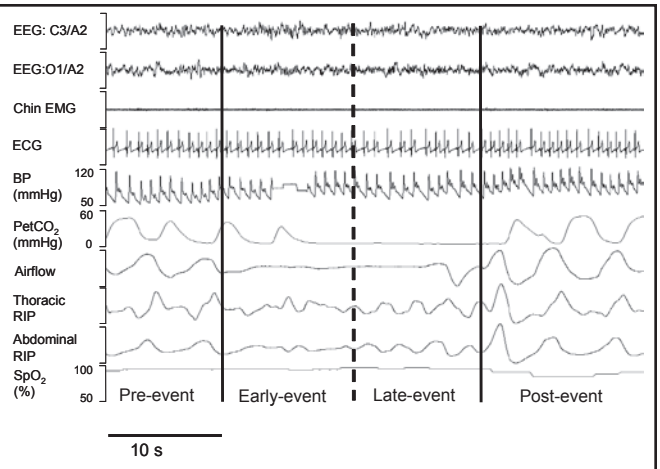

Figure 1—Original polysomnographic trace of an obstructive apnea in REM sleep, indicating the time periods used for cardiovascular analysis. (EEG, electroencephalogram; EMG, electromyogram; ECG, electrocardiogram; BP, blood pressure; $PetCO_2$, end-tidal partial pressure of carbon dioxide; RIP, respiratory inductance plethysmography; SpO_2, oxygen saturation).

Multivariate cluster-wise linear regression was used to determine associations between % change in cardiovascular activity (ΔMAP and ΔHR) from late-event to post-event and sleep state; arousal from sleep (none, subcortical activation, ASDA arousal); O_2 desaturation; length of obstructive event; and severity of SDB (primary snoring [PS], OSA). Furthermore, interaction terms "sleep state × arousal (both subcortical and ASDA)" and "sleep state × O_2 desaturation" were added to the model. For this part of the analysis, data were entered into the model as individual events and clustered by subject to account for repeated observations on individuals. Event related oxygen desaturation (%) and duration of obstructive events were compared between sleep states using Student's *t* tests. The proportions of events terminated with arousal were compared between sleep states using χ^2 analysis. Data are presented as mean ± SEM with statistical significance taken at the $P < 0.05$ level.

RESULTS

The 50 children (28M/22F) originally enrolled in the study and on whom PSG data were collected had a mean age of 9.2 ± 0.2 y and a BMI of 19.9 ± 0.7 kg/m^2. Following PSG, 28 children were diagnosed with PS, 12 with mild OSA, and 10 with moderate/severe OSA. For cardiovascular analysis, obstructive events were excluded where the BP recordings at the time of the event could not be analyzed due to movement artifact or because the events occurred during a cycle of repetitive apneas/hypopneas, and pre-event baselines for HR and BP could not be determined. Subsequently, 20 children (18 PS and 2 mild OSA) were excluded; 9 because none of their events could be analyzed (because of movement artifact or cyclical events), and 11 because they had no obstructive events. There were no anthropometric differences between subjects who were retained or excluded from cardiovascular analysis.

Demographic and polysomnographic data of the 30 children (15M, 15F; 10 PS, 10 mild OSA, 10 moderate/severe OSA) included in the cardiovascular analyses are presented in Table 1.

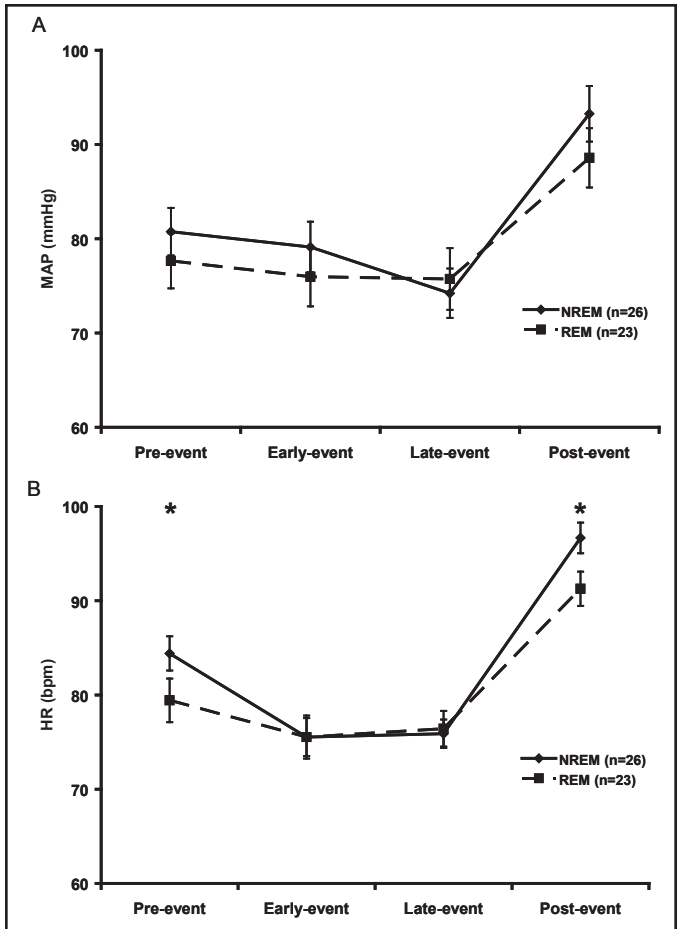

Figure 2—Changes in A) MAP and B) HR during obstructive respiratory events in NREM and REM sleep. *$P < 0.05$ NREM HR compared to REM HR.

Within this group, only 4 children were diagnosed with asthma (1 PS, 1 mild OSA, and 2 moderate/severe OSA). As expected, subjects with OSA had a significantly increased OAHI and a significantly lower SpO_2 nadir than subjects with PS ($P < 0.001$ and $P = 0.008$ respectively). Subjects with OSA also had significantly increased time in stage 1 sleep compared with subjects with PS ($P < 0.05$); and subjects with moderate/severe OSA had significantly increased arousals/h compared with subjects with PS ($P < 0.05$). Systolic and diastolic office BPs were not different between the 3 groups.

Cardiovascular analysis was performed on 614 obstructive events—29 obstructive apneas, 68 mixed apneas, and 517 hypopneas. No MAP or HR differences were found between the 3 groups of children (PS, mild OSA, or moderate/severe OSA), nor between type of obstructive event (apnea or hypopnea) at any time point of the analysis (pre-event, early-event, late-event, or post-event). Therefore, for subsequent cardiovascular analysis all subjects (regardless of severity of SDB) and all obstructive events (regardless of type) were combined.

Changes in Blood Pressure and Heart Rate During Obstructive Events

MAP and HR changes during obstructive events in NREM and REM are presented in Table 2. Of the 30 children, 26 had

Table 1—Subject Demographics and Polysomnographic Characteristics

	PS	Mild OSA	Mod/Severe OSA	ANOVA P
n (males)	10 (5)	10 (6)	10 (4)	ns
Age (y)	10.3 ± 0.5	8.6 ± 0.3*	9.5 ± 0.4	0.033
BMI (kg/m^2)	21.9 ± 1.3	18.3 ± 1.4	23.1 ± 1.8	0.043
BMI z-score	1.3 ± 0.2	0.5 ± 0.4	1.4 ± 0.4	ns
Office BP:				
Systolic (mm Hg)	105 ± 3	106 ± 2	103 ± 2	ns
z-score	0.16 ± 0.28	0.26 ± 0.22	−0.02 ± 0.26	ns
Diastolic (mm Hg)	65 ± 2	61 ± 2	61 ± 2	ns
z-score	0.33 ± 0.22	0.10 ± 0.15	−0.01 ± 0.20	ns
OAHI (events/h)	0.6 ± 0.1	2.5 ± 0.3*	15.2 ± 4.4*†	< 0.001
SpO_2 nadir (%)	91.9 ± 0.9	91.1 ± 0.9	85.1 ± 2.3*†	0.008
TST (h)	6.56 ± 0.29	6.44 ± 0.27	6.15 ± 0.35	ns
Sleep efficiency (%)	85.7 ± 3.3	80.7 ± 3.3	82.0 ± 3.3	ns
% time in stage 1	7.7 ± 0.7	13.0 ± 1.7*	15.3 ± 2.5*	0.01
% time in stage 2	47.0 ± 1.7	41.8 ± 1.8	42.5 ± 1.4	ns
% time in stage 3	5.6 ± 0.7	4.8 ± 0.5	4.8 ± 0.6	ns
% time in stage 4	20.5 ± 1.9	22.9 ± 1.7	21.9 ± 1.3	ns
% time in REM	19.2 ± 1.0	17.4 ± 1.2	15.5 ± 2.4	ns
Arousal index (events/h)	9.9 ± 1.0	14.4 ± 1.6	23.8 ± 3.9*	< 0.001

Values are mean ± SEM. *P < 0.05 compared to PS. †P < 0.05 compared to Mild OSA. PS: primary snoring, OSA: obstructive sleep apnea, BMI: body mass index, BP: blood pressure, OAHI: obstructive sleep apnea hypopnea index, TST: total sleep time. Arousal index = ASDA defined + subcortical activations.

obstructive events in NREM and 23 had obstructive events in REM available for analysis. For events in NREM, MAP was significantly greater post-event compared to pre-event, early-event, and late-event (P < 0.05 for all). In addition, HR significantly decreased from pre-event to early and late-event and then significantly increased post-event (P < 0.05 for all). For obstructive events in REM, both MAP and HR were significantly greater post-event than pre-event, early-event and late-event (P < 0.05 for all).

There was no significant difference in MAP at any time point during obstructive events in NREM compared with events in REM (Figure 2A). However, HR was significantly different during obstructive events between sleep states (P < 0.05, Figure 2B). Post hoc analysis revealed that HR was significantly higher in NREM events than events in REM both pre-event (P < 0.05) and post-event (P < 0.05).

When the changes in MAP and HR between late and post-event were expressed as percentage change (Figure 3), both ΔMAP and ΔHR were significantly greater during obstructive events in NREM (ΔMAP: 26.5% ± 2.5%; ΔHR: 28.1% ± 2.4%) compared to REM (ΔMAP: 18.3% ± 2.4%; ΔHR 20.4% ± 3.0%, P < 0.05 for both).

Determinants of the Change in Blood Pressure and Heart Rate Post Event

Multivariate regression analyses for the % change in MAP and HR from late-event to post-event are presented in Table 3. The NREM sleep state and arousal from sleep (both subcortical activation and ASDA arousal) were significant independent predictors of both the larger % change in MAP and larger % change in HR from late-event to post-event (MAP: NREM sleep state, P < 0.001; Subcortical activation, P < 0.001; ASDA arousal, P < 0.001. HR: NREM sleep state, P = 0.02; Subcortical activation, P < 0.001, ASDA arousal, P < 0.001). Oxygen desaturation, length of respiratory event, and severity of SDB were not significant independent predictors of the cardiovascular change. There were significant interactions between sleep state and arousal (both subcortical activation and ASDA arousal) for the larger % change in MAP (P = 0.01 for both); the negative coefficients indicating that the effect of arousal on MAP was stronger in REM sleep. There was also a significant interaction between the NREM sleep state and oxygen desaturation for the larger % change in HR from late-event to post-event (P = 0.03); a similar trend was seen for the % change in MAP; however, this failed to reach statistical significance (P = 0.09).

Overall, events in REM were associated with significantly larger oxygen desaturations (NREM, 3.0% ± 0.2%; REM, 4.1% ± 0.3%; P = 0.01) and were longer in duration (NREM, 16.4 ± 0.3 s; REM, 19.5 ± 0.5 s; P < 0.001). However, a significantly larger proportion of events in NREM were terminated with arousal—either subcortical activation or ASDA arousal (NREM: no arousal, 9.6%, subcortical activation, 44.5%, ASDA arousal 45.9%. REM: no arousal, 39.1%, subcortical activation 48.3%, ASDA arousal 12.7%. P < 0.001).

DISCUSSION

This study investigated the acute cardiovascular changes occurring during obstructive events in children and reports two major findings: firstly, that children with SDB experience marked perturbations in both BP and HR during and after obstructive events, similar in magnitude to levels reported in adults; and secondly, the surge in cardiovascular activity post-event was more pronounced during NREM sleep and with arousal from sleep.

Studies performed in adult OSA patients measuring BP and HR following an obstructive apnea have reported increases in MAP of approximately 20 mm Hg[20,21] and increases in HR of approximately 15 bpm.[17,20,22] Repetitive increases of this magnitude seen in severe OSA are likely to adversely affect the cardiovascular system by resetting baroreceptors or causing endothelial damage and dysfunction within the microvasculature. Consequently these surges have been implicated in the increased prevalence of hypertension in adults with OSA.[32]

To explicitly compare our BP and HR data with that reported in adults, it is imperative to compare data collected at the end of an obstructive event to that collected post event in the hyperpnea phase. For BP, Garpestad et al.[20] reported an increase in MAP of 20 mm Hg from late to post apnea in adults. Jelic et

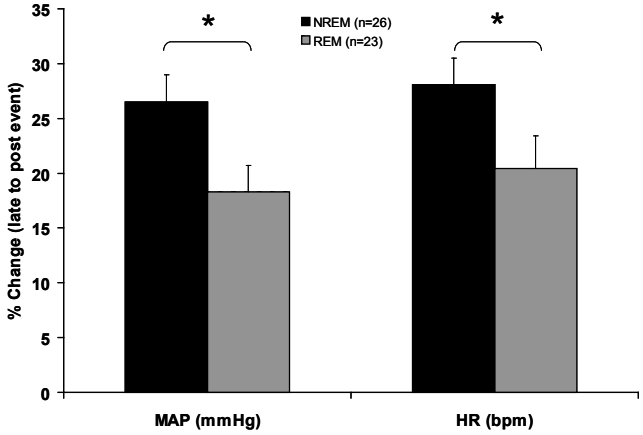

Figure 3—Comparison of % change in MAP and HR at the termination of obstructive events (late-event to post-event) in NREM and REM sleep. *P < 0.05.

Table 2—Mean MAP and HR Values for Obstructive Respiratory Events During NREM (n = 26) and REM Sleep (n = 23)

	Pre-Event	Early-Event	Late-Event	Post-Event
NREM				
MAP (mm Hg)	81 ± 3	79 ± 3	74 ± 3	93 ± 3*†‡
HR (bpm)	84 ± 2	76 ± 2*	76 ± 2*	97 ± 2*†‡
REM				
MAP (mm Hg)	78 ± 3	76 ± 3	76 ± 3	89 ± 3*†‡
HR (bpm)	79 ± 2	76 ± 2	76 ± 2	91 ± 2*†‡

Values are mean ± SEM. *P < 0.05 compared to pre-event. †P < 0.05 compared to early-event. ‡P < 0.05 compared to late-event

al.[22] reported an increase in systolic BP from late to post apnea of 10 mm Hg in NREM and 14 mm Hg in REM. We found in children an increase in MAP of 19 mm Hg in NREM and 13 mm Hg in REM (Δ MAP 26% and 18%, respectively). Garpestad et al.[20] reported an increase in HR of 11 bpm from late to post apnea in adults. Similarly, Jelic et al.[22] reported an increase of 15 bpm, while Stoohs et al.[17] reported an increase of 18 bpm in NREM and 30 bpm in REM. In our patients, we found an increase of 21 bpm in NREM and 15 bpm in REM (Δ HR 28% and 20%, respectively). Although Stoohs et al.[17] reported the peak HR response post event, Garpestad et al.[20] and Jelic et al.[22] averaged BP and HR activity during the hyperpnea phase post event; thus the magnitude of the cardiovascular change may be underreported in these studies. Of note, Imadojemu[16] analyzed BP and HR post event using a method similar method to that in the present study (average of 3 peak values) and reported increases in MAP of 18% and HR of 19% (actual values not reported). Thus, our study has now for the first time demonstrated that children experience large acute perturbations in BP and HR during and after obstructive events that are similar in magnitude to adults.

These acute surges in cardiovascular activity form part of the increased HR and BP variability and decreased nocturnal BP dipping reported in children and may also play a part in the development of hypertension in this group.[6-8,10,11,23] Koyhama et al.[7] reported that BP was significantly correlated with degree of SDB. Similarly, Leung et al.[8] reported higher nocturnal and diurnal BP in children with OSA (> 5 events/h). Amin et al.[6] more recently demonstrated, in a large sample of children, that 24-h ambulatory BP and HR measured every 15 minutes was significantly increased in children with OSA (> 5 events/h) compared with healthy controls. Significantly, this increase in BP predicted cardiac remodeling. In addition, it has been reported that children with OSA have increased levels of brain natriuretic peptide (BNP),[33,34] providing further evidence of acute cardiac strain. BNP is a neurohormone released from cardiac myocytes after cardiac wall distention from volume and pressure overload, as induced by the negative intrathoracic pressure swings and increased peripheral vascular resistance that accompany an obstructive apnea. Until now, however, there have been no reports of beat-by-beat BP and HR in children during sleep. A novel aspect of our study was measurement of the acute changes in BP and HR that occur over a short time period during obstructive events in children with SDB. We demonstrated that these children experienced large fluctuations in BP and HR during obstructive events that may account for the increased measurements and variability during sleep reported by other researchers.

In comparison to adult studies, we had a high proportion of obstructive hypopneas in our data set rather than full obstructive apneas. However, the cardiovascular changes during obstructive events were similar whether they were classified as apneas or hypopneas, and as such, were combined for the purposes of this study. As children with SDB often have more hypopneas rather than frank apneas,[35] investigating the cardiovascular effects of any airway obstruction is important in this group. Previous studies have also combined these events for cardiovascular analysis as apneas and hypopneas induce similar physiological changes (hypercapnia, hypoxia, arousal).[22,36] Furthermore, OSA defined by OAHI has been correlated with cardiovascular disease manifestations in adults,[37] highlighting the fact that hypopneas are as deleterious to the cardiovascular system as apneas. It is also worth noting that our sample of children differs from adults in definition of disease severity. It is widely considered that more than 1 apnea per hour is abnormal in children,[38] while the threshold for OSA in adults is far higher.[39] In addition, 10 children were diagnosed as primary snorers and so were not classified as having OSA. Interestingly however these symptomatic children referred for investigation had similar acute changes in BP and HR over the course of an obstructive event to those with OSA.

Our study has also shown that the surge in cardiovascular activity post-event was associated with presence of arousal from sleep. It is well documented in adults that even spontaneous arousal causes significant cardiovascular changes that are beyond functional requirements.[40] Arousal has also been found to be a strong determinant of cardiovascular changes at the termination of obstructive events in adults. Yoon et al.[36] found that the change in BP post-event was associated with the degree of arousal (duration of EEG change). Similarly, Schneider et al.[41] studied a canine OSA model and found arousal to be a strong determinant of the change in BP and HR post-event. As it has been reported that obstructive events in children are less likely to be terminated by cortical (ASDA defined) arousal than in

Table 3—Predictor Variables of the % Cardiovascular Change from Late-Event to Post-Event: Multivariate Clusterwise Linear Regression

	% Δ MAP			% Δ HR		
	Coeff	β	P	Coeff	β	P
State	9.22	0.31	< 0.001	5.87	0.20	0.02
Arousal						
Subcortical	9.59	0.33	< 0.001	8.66	0.30	< 0.001
ASDA	15.20	0.49	< 0.001	16.31	0.53	< 0.001
O_2 desaturation (%)	0.11	0.03	0.74	0.07	0.02	0.75
Length of event (s)	−0.03	−0.02	0.81	−0.14	−0.06	0.10
Severity of SDB	1.31	0.02	0.70	4.15	0.05	0.27
Interactions						
State × Arousal (subcortical)	−6.06	−0.18	0.01	−2.02	−0.06	0.39
State × Arousal (ASDA)	−7.34	−0.22	0.01	−2.29	−0.07	0.46
State × O_2 desaturation (%)	0.95	0.17	0.09	0.79	0.14	0.03
	$R^2 = 0.24$			$R^2 = 0.31$		

State: In direction of NREM sleep state

adults,[42,43] we designed the present study to compare events terminated with no arousal, subcortical activation, and ASDA arousals. We found that the cardiovascular change post event increased with the increasing levels of arousal. This finding is consistent with reports linking the duration of the arousal from sleep to the associated autonomic response.[44] Thus, while cardiovascular activity increases upon resumption of ventilation, arousal also exerts an influence on the magnitude of the perturbation.

Our study also showed that the surge in cardiovascular activity post-event was more pronounced in the NREM sleep state. Previous studies in adults examining the effect of sleep state on the cardiovascular changes during obstructive respiratory events have yielded conflicting results. The BP and HR profile over the course of an obstructive event in our subjects was similar to that found by Jelic et al.[22] in adult OSA patients; however, they reported no differences between sleep states. On the other hand, Garpestad et al.[45] reported a greater BP elevation post-event during REM in adult OSA patients, although only absolute peak data were reported. Okabe et al.[46] also reported a greater BP elevation post-event during REM in adult OSA patients, however, these events were longer and were associated with greater oxygen desaturation than those in NREM. In our data set, events were also longer and associated with greater desaturation in REM; despite this, we found the overall cardiovascular change to be larger in NREM.

Interestingly, we found a significant association between oxygen desaturation and the change in HR post-event in NREM, but not in REM, despite NREM being associated with smaller desaturations. This finding is in keeping with the increased ventilatory response to hypoxia in NREM compared with REM.[47,48] This increased ventilatory response to hypoxia in NREM could lead to a larger inspiratory effort upon resumption of breathing for an equivalent oxygen desaturation, which could in turn translate to a larger HR response. We speculate then that our larger HR change post-event in NREM could in part be explained by the increased ventilatory sensitivity to hypoxia. This independent effect of sleep state may be not evident in adults due to the reduction in the ventilatory response and cardiac chronotropic response to hypoxia from childhood to adulthood.[49]

In conclusion, this study has demonstrated that children with SDB experience significant changes in HR and BP during obstructive events, similar in magnitude to changes reported in adults. In particular, the large increases in HR and BP at event termination may have important implications for cardiovascular outcome in children with OSA as repetitive obstructive events and cardiovascular perturbations may contribute to the development of hypertension.

ACKNOWLEDGMENTS

The authors would like to thank all children and their parents who participated in this study. The authors would also like to thank Ms Nicole Verginis and all the staff of the Melbourne Children's Sleep Unit for invaluable technical assistance.

Financial Support: NHMRC Project Grant 384142. Dr. O'Driscoll was part-funded by the Kaarene Fitzgerald Fellowship from SIDS & Kids Victoria.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
2. Nixon GM, Brouillette RT. Sleep 8: paediatric obstructive sleep apnoea. Thorax 2005;60:511-6.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
4. Ebert CS Jr, Drake AF. The impact of sleep-disordered breathing on cognition and behavior in children: a review and meta-synthesis of the literature. Otolaryngol Head Neck Surg 2004;131:814-26.
5. Hamilton GS, Solin P, Naughton MT. Obstructive sleep apnoea and cardiovascular disease. Intern Med J 2004;34:420-6.
6. Amin R, Somers VK, McConnell K, et al. Activity-adjusted 24-hour ambulatory blood pressure and cardiac remodeling in children with sleep disordered breathing. Hypertension 2008;51:84-91.
7. Kohyama J, Ohinata JS, Hasegawa T. Blood pressure in sleep disordered breathing. Arch Dis Child 2003;88:139-42.
8. Leung LC, Ng DK, Lau MW, et al. Twenty-four-hour ambulatory BP in snoring children with obstructive sleep apnea syndrome. Chest 2006;130:1009-17.
9. Zintzaras E, Kaditis AG. Sleep-disordered breathing and blood pressure in children: a meta-analysis. Arch Pediatr Adolesc Med 2007;161:172-8.
10. Bixler EO, Vgontzas AN, Lin HM, et al. Blood pressure associated with sleep-disordered breathing in a population sample of children. Hypertension 2008;52:841-6.
11. Li AM, Au CT, Sung RY, et al. Ambulatory blood pressure in children with obstructive sleep apnoea: a community based study. Thorax 2008;63:803-9.

12. O'Brien LM, Gozal D. Autonomic dysfunction in children with sleep-disordered breathing. Sleep 2005;28:747-52.
13. Kaditis AG, Alexopoulos EI, Damani E, et al. Urine levels of catecholamines in Greek children with obstructive sleep-disordered breathing. Pediatr Pulmonol 2009;44:38-45.
14. Nakra N, Bhargava S, Dzuira J, Caprio S, Bazzy-Asaad A. Sleep-disordered breathing in children with metabolic syndrome: the role of leptin and sympathetic nervous system activity and the effect of continuous positive airway pressure. Pediatrics 2008;122:e634-42.
15. Gozal D, Kheirandish-Gozal L, Serpero LD, Sans Capdevila O, Dayyat E. Obstructive sleep apnea and endothelial function in school-aged nonobese children: effect of adenotonsillectomy. Circulation 2007;116:2307-14.
16. Imadojemu VA, Gleeson K, Gray KS, Sinoway LI, Leuenberger UA. Obstructive apnea during sleep is associated with peripheral vasoconstriction. Am J Respir Crit Care Med 2002;165:61-6.
17. Stoohs R, C Guilleminault. Cardiovascular changes associated with obstructive sleep apnea syndrome. J Appl Physiol 1992 72:583-9.
18. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897-904.
19. Schneider H, Schaub CD, Andreoni KA, et al. Systemic and pulmonary hemodynamic responses to normal and obstructed breathing during sleep. J Appl Physiol 1997 83:1671-80.
20. Garpestad E, Katayama H, Parker JA, et al. Stroke volume and cardiac output decrease at termination of obstructive apneas. J Appl Physiol 1992;73:1743-8.
21. Ali NJ, Davies RJ, Fleetham JA, Stradling JR. The acute effects of continuous positive airway pressure and oxygen administration on blood pressure during obstructive sleep apnea. Chest 1992;101:1526-32.
22. Jelic S, Bartels MN, Mateika JH, Ngai P, DeMeersman RE, Basner RC. Arterial stiffness increases during obstructive sleep apneas. Sleep 2002;25:850-5.
23. Constantin E, CD McGregor, V Cote, Brouillette RT. Pulse rate and pulse rate variability decrease after adenotonsillectomy for obstructive sleep apnea. Pediatr Pulmonol 2008 43:498-504.
24. Groner JA, Joshi M, Bauer JA. Pediatric precursors of adult cardiovascular disease: noninvasive assessment of early vascular changes in children and adolescents. Pediatrics 2006 118:1683-91.
25. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004 114:555-76.
26. Ogden CL, Kuczmarski RJ, Flegal KM, et al. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. Pediatrics 2002;109:45-60.
27. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects. Washington DC: U.S. Government Printing Office, 1968.
28. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173-84.
29. Mograss MA, Ducharme FM, Brouillette RT. Movement/arousals. Description, classification, and relationship to sleep apnea in children. Am J Respir Crit Care Med 1994;150:1690-6.
30. Iber C, Ancoli-Israel S, Chesson A, Quan S. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester, IL: American Academy of Sleep Medicine, 2007.
31. Standards and indications for cardiopulmonary sleep studies in children. American Thoracic Society. Am J Respir Crit Care Med 1996;153:866-78.
32. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378-84.
33. Sans Capdevila O, Crabtree VM, Kheirandish-Gozal L, Gozal D. Increased morning brain natriuretic peptide levels in children with nocturnal enuresis and sleep-disordered breathing: a community-based study. Pediatrics 2008;121:e1208-14.
34. Kaditis AG, Alexopoulos EI, Hatzi F, et al. Overnight change in brain natriuretic peptide levels in children with sleep-disordered breathing. Chest 2006;130:1377-84.
35. Rosen CL, D'Andrea L, Haddad GG. Adult criteria for obstructive sleep apnea do not identify children with serious obstruction. Am Rev Respir Dis 1992;146:1231-4.
36. Yoon IY, Jeong DU. Degree of arousal is most correlated with blood pressure reactivity during sleep in obstructive sleep apnea. J Korean Med Sci 2001;16:707-11.
37. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19-25.
38. Marcus CL, Omlin KJ, Basinki DJ, et al. Normal polysomnographic values for children and adolescents. Am Rev Respir Dis 1992;146:1235-9.
39. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667-89.
40. Trinder J, Allen N, Kleiman J, et al. On the nature of cardiovascular activation at an arousal from sleep. Sleep 2003;26:543-51.
41. Schneider H, Schaub CD, Chen CA, et al. Effects of arousal and sleep state on systemic and pulmonary hemodynamics in obstructive apnea. J Appl Physiol 2000;88:1084-92.
42. McNamara F, Issa FG, Sullivan CE. Arousal pattern following central and obstructive breathing abnormalities in infants and children. J Appl Physiol 1996;81:2651-7.
43. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2004;169:623-33.
44. Pitson D, Chhina N, Knijn S, van Herwaaden M, Stradling J. Changes in pulse transit time and pulse rate as markers of arousal from sleep in normal subjects. Clin Sci (Lond) 1994;87:269-73.
45. Garpestad E, Ringler J, Parker JA, Remsburg S, Weiss JW. Sleep stage influences the hemodynamic response to obstructive apneas. Am J Respir Crit Care Med 1995;152:199-203.
46. Okabe S, Hida W, Kikuchi Y, et al. Role of hypoxia on increased blood pressure in patients with obstructive sleep apnoea. Thorax 1995;50:28-34.
47. Marcus CL, Lutz J, Carroll JL, Bamford O. Arousal and ventilatory responses during sleep in children with obstructive sleep apnea. J Appl Physiol 1998;84:1926-36.
48. Douglas NJ, White DP, Weil JV, et al. Hypoxic ventilatory response decreases during sleep in normal men. Am Rev Respir Dis 1982 125:286-9.
49. Marcus CL, Glomb WB, Basinski DJ, Davidson SL, Keens TG. Developmental pattern of hypercapnic and hypoxic ventilatory responses from childhood to adulthood. J Appl Physiol 1994;6:314-20.