The heart rate response to spontaneous arousal from sleep is reduced in children with Down syndrome referred for evaluation of sleep-disordered breathing

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The heart rate response to spontaneous arousal from sleep is reduced in children with Down syndrome referred for evaluation of sleep-disordered breathing. Am J Physiol Heart Circ Physiol 298: H1986–H1990, 2010. First published March 26, 2010; doi:10.1152/ajpheart.00701.2009.—Arousal from sleep in healthy adults is associated with a large, transient increase in heart rate (HR). Individuals with Down syndrome (DS) have attenuated cardiovascular responses to autonomic tests during wakefulness. We tested the hypothesis that the HR response to arousal from sleep is reduced in children with DS and obstructive sleep apnea (OSA) compared with healthy children. Twenty children aged 3–17 yr referred for investigation of sleep-disordered breathing (10 DS, and 10 OSA controls) matched for age and obstructive apnea/hypopnea index underwent routine overnight polysomnography. In addition, 10 non-snoring controls from the general community were studied. Beat-by-beat HR was analyzed from 15 s pre- to 15 s post-spontaneous arousals and compared between groups using two-way ANOVA with repeated measures. Data are presented as means ± SE. For both rapid eye movement (REM) and non-REM (NREM), arousals were associated with a significant increase in HR in all groups (peak response NREM: DS, 118 ± 1% at 3 s; OSA controls, 124 ± 2% at 4 s; and healthy controls, 125 ± 3% at 4 s; and peak response REM: DS, 116 ± 2% at 4 s; OSA controls, 123 ± 3% at 4 s; and healthy controls, 125 ± 4% at 4 s; P < 0.001 for all). Post hoc analysis revealed that HR in the DS group was significantly lower than both control groups at 1–4 s in NREM and at 4 to 5 s in REM (P < 0.05 for all). In conclusion, the HR response to spontaneous arousal from sleep is reduced in children with DS and OSA compared with healthy children. This attenuated cardiovascular response could be due to reduced sympathetic activation or blunted vagal withdrawal and may have implications for the child with DS and OSA.

autonomic control; pediatric

DOWN SYNDROME (DS), caused by an extra copy of chromosome 21 (Trisomy 21), is the single most common genetic condition in humans. Individuals with DS appear to have reduced cardiovascular responsiveness. Studies performed during wakefulness have consistently reported that adults with DS have attenuated heart rate (HR) and blood pressure (BP) responses to autonomic challenges such as exercise tests (4, 18), isometric handgrips (16), cold pressor tests (14), and orthostatic challenges (12). In addition, exercise-induced maximal HR has been shown to be reduced in children with DS (5, 13). These reduced responses may be due to inadequate sympathetic activation or blunted vagal withdrawal. This reduced cardiovascular responsiveness, which is independent of obesity (14), has led to the suggestion that individuals with DS exhibit autonomic dysfunction, which itself is associated with increased morbidity and mortality (23). To date, cardiovascular responses in individuals with DS have only been examined during wakefulness.

It has been well documented that arousal from sleep is associated with cardiorespiratory activation. Arousal causes large transient increases in HR, BP, and ventilation that are beyond functional requirements (3, 40). In the healthy individual, the magnitude of the cardiorespiratory response to arousal from sleep is remarkably consistent and is not altered by chemoreceptor or upper airway mechanoreceptor stimulation (7, 29, 30). Autonomic blockade studies performed in dogs have shown that arousal from sleep is associated with both acute cardiac sympathetic activation as well as parasympathetic withdrawal (20).

Given the autonomic studies performed in individuals with DS during wakefulness, we reasoned that reduced cardiovascular responsiveness would also be present in this group during sleep. The cardiovascular response to arousal from sleep serves an important protective purpose, particularly in obstructive sleep apnea (OSA), by restoring airway patency and oxygenation (19). Inadequate cardiovascular responsiveness during sleep would be detrimental in DS since it could further exacerbate the acute negative impacts of apnea and hypoxia (24, 35, 38), which together form the hallmark of OSA. This response is particularly important given that the prevalence of OSA in children with DS is ~60% (9, 25, 28, 39) compared with 1–3% in the general pediatric population (17, 34). Therefore, we aimed to test the hypothesis that the HR response to spontaneous arousal from sleep is reduced in children with DS and OSA compared with otherwise healthy children with and without OSA.

METHODS

The Monash University and Southern Health Human Research Ethics Committees granted ethical approval for this project. Written informed consent was obtained from parents before commencement of the clinical study to use the sleep study and any demographic data for future research purposes, and no monetary incentive was provided for participation.

Subjects. This was a retrospective study of 30 children (aged 3–17 yr): 10 children with DS (4 boys and 6 girls) referred for investigation of sleep disordered breathing, 10 otherwise healthy children (6 boys
and 4 girls) referred for investigation of sleep disordered breathing, and 10 nonsnorers control children (2 boys and 8 girls). The nonsnooring control children were recruited from the general population as part of a larger study and had no history of OSA as determined by medical history and confirmed by polysomnography (PSG); therefore, these children were a nonreferred group. The otherwise healthy children were identified from a list of children with OSA and no other comorbidities (OSA controls). An individual match was located for each child with DS based on age (mean difference, 0.8 ± 0.2 yr) and severity of OSA (mild or moderate/severe, see Data analysis for definitions). No child had a history of congenital heart disease or thyroid dysfunction. All children were healthy at the time of the study and were receiving no medication.

**Protocol.** All children underwent routine overnight PSG using a commercially available PSG system (Series S Sleep System, Compumedics, Melbourne, Australia). Electroencephalograms (EEG: C4/A1, O2/A1), electrooculograms (EOG: left and right outer canthus), electrocardiogram (ECG), electrocerephalogram (EMG: submentalis muscle), electromyograms (EMG: left and right leg EMG, and body position were recorded. Oxygen transcutaneous carbon dioxide (TCM3, Radiometer, Copenhagen, Denmark) and end-tidal carbon dioxide (Capnocheck Plus, BCI, Waukesha, WI) and thoracic and abdominal breathing movements were recorded via uncalibrated respiratory inductance plethysmography (z-RIP belts, Pro-Tech Services, Mukilteo, WA). Both end-tidal carbon dioxide (Capnocheck Plus, BCI, Waukesha, WI) and transcutaneous carbon dioxide (TCM3, Radiometer, Copenhagen, Denmark) were recorded, and airflow was measured via nasal pressure and oronasal thermistor (Compumedics). Following the PSG study, data were transferred via European data format to data analysis software (Chart 5, ADInstruments, Sydney, Australia) for detailed cardiovascular analysis. Before PSG, height and weight were recorded and body mass index (BMI) was calculated. To account for the effect of age and sex difference, the BMI was converted to a z-score according to published criteria (31).

**Data analysis.** Sleep was scored from the EEG, EOG, and chin EMG channels in 30-s epochs according to standard criteria (33). Respiratory events ≥2 respiratory cycles in duration were scored. Obstructive apneas, mixed apneas, and hypopneas were defined according to standard criteria (hypopnea desaturation criterion ≥3%) (2). 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. The diagnostic criteria for the classification of OSA severity following current clinical practice were as follows: children were categorized as having mild OSA (OAHI between 1 and 5 events/h) or moderate/severe OSA (OAHI > 5 events/h).

Arousals were scored according to the guidelines of the American Sleep Disorders Association (1); i.e., an abrupt shift in EEG frequency lasting >3 s (including any combination of theta, alpha or other activity > 16 Hz but not spindle or delta frequencies). Subcortical activations were also scored when ≥2 of the following events occurred and met criteria described by Mograss et al. (26): an increase in EMG and an increase in HR or a body movement (i.e., autonomic arousals not meeting American Sleep Disorders Association criteria). Arousals and subcortical activations were combined to give a total arousal index. Arousals included in the cardiovascular analysis fulfilled all of the following criteria: 1) spontaneous American Sleep Disorders Association-defined arousals from rapid eye movement (REM) or non-REM (NREM) 2–4, 2) arousal duration ≥ 3 s and < 15 s (measured from the EEG), and 3) arousals preceded by a minimum of 30 s stable sleep ensure a stable HR baseline (i.e., no arousals or respiratory events were present).

Beat-by-beat HR was analyzed from 15 s before arousal to 15 s after arousal and resampled at 1-s intervals using linear interpolation to enable a comparison between groups. Values were averaged for each child to ensure they contributed equally to the group mean; i.e., all arousals from an individual child were averaged in each sleep state and the final HR arousal trend was added to the group data. HR data are presented as percent change from baseline (100%). HR baseline was taken as the average from −15 to −6 s before the arousal. This 10-s window was chosen for the baseline to ensure that any prearousal changes from −5 s onward were not missed (37). To identify the break point in the HR trend (the point where the HR starts to increase), we used an analytical process based on bilinear regression to identify the point where the residual sums of squares of both regression lines together reach a nadir (i.e., where the intersecting lines best fit the data) (27, 41).

**Statistical analysis.** Statistical analysis was performed using Sigma Stat (version 3.0, SPSS). Subject demographics and polysomnographic characteristics (including mean arousal duration) were compared between groups using one-way analysis of variance with Bonferroni post hoc testing. The proportions of boys and girls and subjects with mild and moderate/severe OSA were compared between groups using χ² analysis. To determine whether the HR trend over the course of arousal in the DS group was significantly different between those of the two control groups, the HR trends in both sleep states were compared separately between the DS and OSA controls and the DS and healthy control groups using two-way repeated-measure analyses of variance (time × group) with Student-Newman-Keuls post hoc testing. The data tested were from −6 to 5 s relative to arousal (time 0) to capture the peak HR response of all subjects. All data are presented as means ± SE. Statistical significance was taken at the P < 0.05 level.

**RESULTS**

Subject demographics and polysomnographic characteristics are presented in Table 1. Statistical comparison confirmed there was no difference between the groups for sex, age, BMI, or BMI z-score. In addition, there were no significant differences between groups for sleep efficiency or percent time spent in NREM and REM. Similarly, there was no difference in the baseline HR between groups or between sleep states before the arousal. Significant differences between groups lie in the OAHI and arousal index with the OSA groups having significantly increased indexes compared with the healthy controls (P < 0.05 for all). In the OSA groups, all children had OSA defined as >1 obstructive event/h, with equal numbers of children being classified as having mild OSA and moderate/severe OSA.

<table>
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<th>Table 1. Subject demographics and polysomnographic data</th>
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<td><strong>Age, yr</strong></td>
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Values are means ± SE; n, number of subjects; DS, Down syndrome; OSA, obstructive sleep apnea; BMI, body mass index; REM, rapid eye movement; NREM, non-REM; OAHI, obstructive apnea/hypopnea index; SaO2, oxygen saturation. *P < 0.05 vs. healthy controls.
HR response to arousal in NREM. A total of 296 arousals were analyzed from NREM (4–24 per subject). Mean arousal duration was not different between groups (DS, 7.4 ± 0.4 s; OSA controls, 8.3 ± 0.3 s, and healthy controls, 7.3 ± 0.3 s; P > 0.05). The mean HR trend over the course of arousal during NREM for all groups is shown in Fig. 1. There was a significant increase over time in all groups (P < 0.001), peaking at 4 s for all groups, followed by a decline to prearousal levels. In this sleep state, HR dipped below prearousal levels before restabilizing. Whereas there was no overall difference between the DS group and OSA controls (P = 0.19), there was a significant “time × group” interaction (P < 0.05). Post hoc analysis revealed that HR in the DS group was significantly lower compared with that in the OSA controls at 3–5 s (P < 0.05 for all). Similarly, when the DS group and healthy controls were compared, there was a significant “time × group” interaction (P < 0.05). Post hoc analysis revealed that HR in the DS group was significantly lower compared with that in the healthy controls at 4–5 s (P < 0.05 for both). With the use of break-point analysis, the increase in HR preceded the onset of the arousal in all groups (DS, −4 s; OSA controls, −3 s; and healthy controls, −3 s).

The mean SaO2 remained constant pre- and postarousal in all groups [DS, 96.0 ± 0.7% (pre) and 95.9 ± 0.6% (post); OSA controls, 97.2 ± 0.4% (pre) and 97.0 ± 0.3% (post); and healthy controls, 98.0 ± 0.4% (pre) and 97.9 ± 0.4% (post)].

HR response to arousal in REM. A total of 91 arousals were analyzed from REM in eight children with DS, eight OSA controls, and eight healthy controls (1–9 per subject). The remaining six children did not have any spontaneous arousals, fulfilling the inclusion criteria in this sleep state. Mean arousal duration was not different between groups (DS, 6.5 ± 0.4 s; OSA controls, 7.1 ± 0.6 s, and healthy controls, 6.8 ± 0.7 s; P > 0.05). The mean HR trend over the course of arousal during REM for all groups is shown in Fig. 2. There was a significant increase over time in all groups (P < 0.001), peaking at 4 s for all groups, followed by a decline to prearousal levels. In this sleep state, HR dipped below prearousal levels before restabilizing. Whereas there was no overall difference between the DS group and OSA controls (P = 0.19), there was a significant “time × group” interaction (P < 0.05). Post hoc analysis revealed that HR in the DS group was significantly lower compared with that in the OSA controls at 3–5 s (P < 0.05 for all). Similarly, when the DS group and healthy controls were compared, there was a significant “time × group” interaction (P < 0.05). Post hoc analysis revealed that HR in the DS group was significantly lower compared with that in the healthy controls at 4–5 s (P < 0.05 for both). With the use of break-point analysis, the increase in HR preceded the onset of the arousal in all groups (DS, −4 s; OSA controls, −3 s; and healthy controls, −3 s).

The mean SaO2 remained constant pre- and postarousal in all groups [DS, 95.1 ± 0.7% (pre) and 95.3 ± 0.6% (post); OSA controls, 96.7 ± 0.7% (pre) and 96.7 ± 0.4% (post); and healthy controls, 97.8 ± 0.5% (pre) and 97.7 ± 0.5% (post)].

**DISCUSSION**

The major finding of this study is that children with DS have a reduced HR response to spontaneous arousal from sleep compared with otherwise healthy children matched for age and severity of OSA and healthy control children without OSA. This reduced HR response was evident in both NREM and REM sleep.

In keeping with our new information, there have been many reports detailing attenuated autonomic responses in the DS population. Guerra et al. (18) reported that the peak HR during maximal treadmill exercise tests was lower in individuals with DS compared with healthy controls. Low maximal HRs are the hallmark of chronotropic incompetence, a condition that is related to overt coronary heart disease (23) and heart failure (22). Fernhall et al. (12) showed that individuals with DS exhibited a blunted HR response to upright tilt despite an increase in BP, a response consistent with reduced sympathetic excitation. Further supporting the notion of a reduced sympathetic response in this group, Eberhard et al. (10) reported that the rise in circulating catecholamines in response to incremental exercise was reduced in individuals with DS. More recently it has been shown that there is little to no change in catecholamine levels with maximal exercise in those with DS (11).

Additionally, HR and BP responses to both the cold pressor test and isometric handgrip test during wakefulness were reported by Fernhall et al. (14) to be reduced in individuals with DS compared with healthy controls. Whereas a reduction in the cardiovascular response to the cold pressor test indicates reduced sympathetic activation, a reduction in the response to the handgrip indicates both reduced sympathetic activation and blunted vagal withdrawal. Of note, the cardiovascular responses were reduced even after controlling for obesity in the group with DS. Similarly, Figueroa et al. (16) found the attenuated HR and BP responses to isometric handgrip in individuals with DS to be independent of obesity.

In support of these studies, we have shown for the first time that the HR response to arousal from sleep is reduced in...
children with DS and OSA compared with their otherwise healthy counterparts. Arousal from sleep is associated with both sympathetic activation and parasympathetic withdrawal (20). Whether the reduced HR response in the children with DS and OSA in our study is a consequence of reduced sympathetic activation or blunted vagal withdrawal or both can only be definitively answered by autonomic blockade studies.

We found the HR increase at arousal from sleep preceded the cortical change in both groups. This anticipatory phenomenon associated with spontaneous arousal has been well described in the literature. Studies have consistently described HR acceleration before EEG arousal (6, 36, 37, 40), supporting the concept that cardiac sympathetic activation precedes the arousal at the cortex. Of note, Sforza et al. (37) demonstrated that this early HR acceleration is mirrored by an increase in EEG activity across the spectra (from delta to beta frequencies), suggesting a concomitant early neural change before the EEG arousal. Therefore, HR acceleration before EEG changes is consistent with a central process heralding or possibly driving the EEG activation. As the autonomic control of cardiovascular activity is mediated by areas within the medulla (8), anatomic abnormalities within the brain stem have been suggested as the source of autonomic dysfunction in DS (21). While we found the overall response to be dampened supporting this view, the HR acceleration before the EEG activation appears to be intact in children with DS, suggesting that this particular central process is not abolished by the genetic abnormality.

The autonomic response to arousal from sleep serves an important protective purpose, particularly in OSA. Acutely, large cardiovascular and ventilatory responses at apnea termination serve to reestablish airway patency and restore oxygenation, providing important protection against hypoxemia. We have shown that children with DS have a reduced cardiovascular response most likely due to autonomic dysfunction (e.g., dampened sympathetic activity). We do not have a quantitative measure of ventilation in our subjects because this would require them to wear a face mask and pneumotachograph during sleep. This technique is challenging in the healthy adult and is not feasible in the developmentally disabled child. However, exercise testing in individuals with DS during wakefulness has shown that the reduced cardiovascular response in DS accompanies a reduced ventilatory response (4, 15, 18). Low maximal ventilation in these studies accompanies reduced peak oxygen uptake, suggesting a low work capacity. In any case, the cardiovascular and ventilatory response postapnea may still be inadequate, a combined deficit that may be detrimental in this group.

**Implications.** We speculate that in children with DS and OSA, these reduced cardiovascular and ventilatory responses may exacerbate acute hypoxic exposure. In this situation the cardiorespiratory compensations are limited, reoxygenation may be slower and arterial hypoxemia may be prolonged following apnea termination. Increased hypoxic exposure may be particularly detrimental in children with DS given the increased prevalence of pulmonary hypertension in this group (25, 35). In light of this, future research should be aimed at investigating the acute cardiorespiratory changes during and at the termination of hypoxia-inducing apnea to elucidate the effect that OSA has on the child with DS.

**Limitations.** The main limitation of the current study is the small sample size, a reflection on the number of children with DS referred for investigation of sleep-disordered breathing with no other comorbidity. Congenital heart disease and thyroid dysfunction are common in this population (32); however, no child in our sample had a history of either condition. Furthermore, care was taken to match the subjects according to age and OSA severity. Despite this, it should be taken into account that the number of patients studied may have been too low to exclude a type 2 error in the demographic and polysomnographic variables presented in Table 1. Specifically, the 0.8-yr mean difference in age between individual matches of children with OSA, the sex distributions across groups, and the differences in OAI, while similar and not statistically different, may not nullify any real group differences given the sample size. It is possible, then, given this limitation, that the study may be open to a referral bias.

A further limitation of the current study is the lack of a control group with DS (i.e., children with DS without OSA recruited from the general population). However, we predict that the HR response to spontaneous arousal from sleep in children with DS without OSA is also dampened. This prediction is based on the fact that the presence and severity of OSA has no bearing on the HR response to “spontaneous arousal.” While the HR response to an arousal after an obstructive apnea is large, the presence of the OSA condition does not augment the response to a spontaneous arousal (one without any prior breathing disturbance). Thus the HR response to a spontaneous arousal is a fixed response. This has been demonstrated in adults (7, 29, 30, 40), and importantly, this is also demonstrated in our two groups of children without DS.

In conclusion, our study demonstrates that children with DS and OSA have a reduced HR response to arousal from sleep. This attenuated cardiovascular response may be due to reduced sympathetic activation or blunted vagal withdrawal and may have implications for the child with DS and OSA.

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HEART RATE CHANGES IN DOWN SYNDROME

GRANTS
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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES