CLINICAL RESEARCH ARTICLE

Children with Down syndrome and sleep disordered breathing have altered cardiovascular control

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BACKGROUND: Sleep disordered breathing (SDB) in typically developing (TD) children is associated with adverse cardiovascular effects. As children with Down syndrome (DS) are at increased risk for SDB, we aimed to compare the cardiovascular effects of SDB in children with DS to those of TD children with and without SDB.
METHODS: Forty-four children with DS (3–19 years) were age and sex matched with 44 TD children without SDB (TD−) and with 44 TD children with matched severity of SDB (TD+). Power spectral density was calculated from ECG recordings, for low frequency (LF), high frequency (HF), total power and the LF/HF ratio.
RESULTS: Children with DS had lower HF power, and higher LF/HF during sleep and when awake. There were no differences between groups for LF power. SpO_2 nadir, average SpO_2 drop and $SpO_2 > 4\%$ drop were larger in the DS group compared to the TD+ group ($p < 0.05$ for all).
CONCLUSIONS: Our findings demonstrate significantly reduced parasympathetic activity (reduced HF power) and increased LF/HF (a measure of sympathovagal balance) in children with DS, together with greater exposure to hypoxia, suggesting SDB has a greater effect in these children that may contribute to an increased risk of adverse cardiovascular outcomes.

IMPACT:

- Sleep disordered breathing in children with Down syndrome exacerbates impaired autonomic control and increases exposure to hypoxia, compared to typically developing children.
- In typically developing children sleep disordered breathing has adverse effects on autonomic cardiovascular control.
- The prevalence of sleep disordered breathing is very high in children with Down syndrome; however, studies on the effects on cardiovascular control are limited in this population.
- This study supports screening and early treatment of sleep disordered breathing in children with Down syndrome.

INTRODUCTION

Down syndrome (DS) is the most common human chromosomal disorder, with an annual incidence of 1 in 400–1500 live births annually worldwide.[1] Better care and medical treatment have led to a significant increase in average life expectancy of persons with DS in developed countries.[2] Optimizing the health of children with DS to enhance quality of life, and identifying problems that could lead to secondary complications as early as possible are of the utmost importance.

Distinct dysmorphic features, such as mid-face and mandibular hypoplasia, relatively large and medially positioned tonsils, and macroglossia, result in a significant reduction in the size of the upper airway in children with DS when compared to typically developing (TD) children.[3,4] Additionally, the obesity and generalized hypotonia, which are also common in DS, contribute to the collapse of the upper airway during sleep and contribute significantly to respiratory compromise manifest as sleep disordered breathing (SDB).[4,5]

SDB has a spectrum of severity from primary snoring at the mild end to obstructive sleep apnea (OSA). The incidence of OSA is far higher in children with DS, where the condition has been found in 31–97% depending on the patient selection criteria, definitions and methodologies used,[6–15] compared to TD children, where 1–6% are affected.[16] Given this increased prevalence of OSA in children with DS, the American Academy of Pediatrics recommends that all children with DS have an overnight polysomnographic (PSG) study by the age of 4 years, as significant OSA may be present in these children despite the lack of parental report of symptoms.[17] However, PSG is difficult to access in many countries, and may be poorly tolerated in young children, particularly those with intellectual disability.

TD children with SDB have adverse cardiovascular impacts, including elevated heart rate and blood pressure (BP), and decreased control of both heart rate (HR) and BP.[18] We have previously shown that the HR response at spontaneous arousal from sleep[19] and to respiratory events[20] are dampened in children

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with DS and SDB compared to TD children. In addition, the time to resaturation post-event was significantly increased, suggesting autonomic dysfunction in children with DS, which may place this group uniquely at risk for cardiovascular complications.[20] To date there have been limited studies investigating the cardiovascular consequences of SDB in children with DS[19–22] and only one small study has examined heart rate variability (HRV) as a measure of autonomic control.[21]

HRV measures the beat-by-beat changes in heart rate from the R-R intervals on the electrocardiogram. Power spectral analysis of the R-R intervals separates HRV into low frequency (LF) power, reflecting both sympathetic and parasympathetic activity, high frequency (HF) power, reflecting parasympathetic activity, and the ratio of low to high frequency (LF/HF) power. The LF/HF ratio is commonly interpreted as an indication of sympathovagal balance,[23] although this is not accepted by all authors.[24] There is a nonlinear relationship between parasympathetic and sympathetic activity, and thus a change in the LF/HF cannot be interpreted from a direct change in either activity.

The aim of this study was to compare the cardiovascular effects of SDB in children with DS to those of TD children with and without SDB. We hypothesized that children with DS would have impaired cardiovascular control compared to TD children matched for SDB severity.

METHODS

Ethical approval for this study was obtained from the Monash University and Monash Health Human Research Ethics Committees (12276B, 14024B, 15048A). Written consent was obtained from parents and verbal assent from children.

Children with DS (aged 3–19 years) were recruited from the community ($n = 24$) and from those referred for clinical assessment of SDB at the Melbourne Children's Sleep Centre ($n = 20$) between May 2016 and March 2018. Control non-snoring TD children matched for age and sex, and TD children with SDB matched for obstructive apnea hypopnea index (OAHI), age and sex were selected from our research database of TD children studied between June 2013 and December 2016. Non-snoring TD control children were recruited from the community and the TD children with SDB were clinically referred for assessment of SDB. All TD children were born at term and were otherwise healthy with no comorbidities such as craniofacial syndromes, developmental disability or genetic syndromes as assessed by the referring clinician. Both TD and children with DS were well at the time of the PSG study and none of the TD children was taking medications known to affect sleep or breathing. Of the children with DS, 3 had undergone heart surgery as an infant but were considered to have no cardiology problems at the time of the study, 12 had undergone an adenotonsillectomy, 9 were on thyroxine for hypothyroidism and 2 were taking melatonin for sleep.

All children underwent overnight attended PSG using standard pediatric recording techniques.[25,26] Prior to the PSG study, height and weight were measured and body mass index (BMI) z score calculated.[27] Obesity was defined as ≥95th percentile (BMI z scores ≥ 1.65) and overweight as ≥85th percentile (BMI z scores ≥ 1.04). Office BP was measured in triplicate during quiet wakefulness (Dinamap V100, CARESCAPETM, Freiburg, Germany) with an appropriately sized cuff. Systolic and diastolic BP measurements were normalized to account for age and height and a z score and percentage calculated (https://www.bcm.edu/bodycomplab/Flashapps/BPVAgeChartpage.html). BP ≥ 95th percentile suggests the child has hypertension and 90th < 95th percentile suggests prehypertension.

Electrophysiological signals were recorded using a commercially available PSG system (E-Series or Grael, Compumedics, Melbourne, Australia) as previously published.[28] In brief,

electroencephalogram (EEG) (Cz, F3-A2, F4-A1, C3-A2, C4-A1, O1-A2, O2-A1), right and left electroocculogram (EOG), submental electromyogram (EMG), left and right anterior tibialis muscle EMG, and electrocardiogram (ECG). Respiratory characteristics were captured using abdominal and thoracic respiratory plethysmography (Pro-Tech zRIP™ Effort Sensor, Pro-Tech Services Inc., Mukilteo, WA, USA), oronasal thermistor, nasal pressure and transcutaneous carbon dioxide ($TcCO_2$) (TCM4/40, Radiometer, Denmark, Copenhagen or Sentec, Therwil, Switzerland). Peripheral oxygen saturation (SpO_2) was measured using Bitmos GmbH (Bitmos, Dusseldorf, Germany), which uses Masimo signal extraction technology for signal processing or Masimo Radical 7 (Masimo, Irving, CA, USA), with both devices set to a 2-s averaging time. All PSG studies were scored manually in 30-s epochs for sleep stages (N1, N2, N3 and REM), respiratory events > 2 breaths in duration and arousals by trained pediatric sleep technicians using Compumedics ProFusion software according to American Academy of Sleep Medicine pediatric guidelines.[25,26] The OAHI, defined as the total number of obstructive apneas, mixed apneas, obstructive hypopneas per hour of total sleep time (TST), was used to define SDB severity. Other respiratory parameters included the central apnea hypopnea index (CnAHI) defined as the number of central apneas and hypopneas per hour of TST, SpO_2 nadir, the ODI4% defined as the number of times the SpO_2 dropped by greater than or equal to 4% per hour of TST, ODI90% defined as the number of times the SpO_2 dropped below 90% per hour of TST, and the average transcutaneous pCO_2 during TST.

For HRV analysis, PSG data were transferred via European Data Format to data analysis software (LabChart 7.1, ADInstruments, Sydney, Australia). Every 2-min epoch from the entire overnight study (including respiratory events) that was free of movement artifact (disruption to the ECG signal caused by gross body movement) on the ECG signal was selected. Periods of wakefulness during the sleep period were excluded. Each 2-min epoch was separated from the previous epoch by at least 30 s.[29] The intervening 30-s epochs were ECG artifact free. The 2-min epochs were then grouped into wake before sleep onset and all epochs of sleep (N2, N3 and REM) across the night and a mean value for each state (wake and sleep) calculated for each subject. A minimum of 10 min of HRV data for each state was required for inclusion in analysis.[29] The data were not filtered to exclude respiratory events as we have previously shown in TD children that HRV does not change between periods of stable sleep and sleep containing respiratory events.[29,30]

The power spectral densities for the LF (0.04–0.15 Hz) reflecting a mixture of both parasympathetic and sympathetic activity, and HF (0.15–0.4 Hz) reflecting parasympathetic activity, bands were determined.[23] Total power (TP) reflects overall automatic activity. The LF/HF ratio was determined as a measure of sympathovagal balance. The LF/HF ratio was used rather than normalized LF and HF values as the normalized values are mathematically equivalent to the LF/HF ratio and do not add information over and above that measure.[31]

Statistical analysis

Statistical analysis was carried out in SigmaPlot (SigmaPlot Version 14.0, Systat Software, San Jose, CA). Data were first tested for normality and equal variance. Demographic, sleep, and respiratory data were not normally distributed and were compared between the three groups with Kruskal−Wallis one way analysis of variance (ANOVA) with Dunn's post hoc testing. HRV data were log transformed and compared with two-way ANOVA with post hoc Student−Newman−Keuls testing to assess the effects of group and sleep state. Proportions were compared between groups with Fisher's exact test. Correlations between HRV parameters and OAHI were carried out using Pearson's correlation analysis. Data are presented as median and interquartile range for demographic, sleep and respiratory data and mean ± standard error of the mean

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(SEM) for HRV data. A p value of <0.05 was considered statistically significant.

RESULTS

Forty-four children with DS were recruited and matched for age and gender with 44 TD children without SDB (TD−) and 44 children matched for age, sex and SDB severity (TD+). Demographic data are compared between the three groups in Table 1. The median age of the children studied was 8 years (range 3–19 years). By design, there were no differences in age or sex between the groups. BMI z score was not different between the DS and TD+ groups but was higher in the DS group compared to the TD− group ($p < 0.01$). Similarly the proportion of children who were obese or overweight did not differ between the DS and TD+ groups; however, there were fewer obese children in the TD− group compared to both DS and TD+ groups ($p < 0.05$ for both) and fewer overweight children in the TD− group compared to the TD+ group ($p < 0.05$). Neck, waist and hip circumferences were not different between the three groups. There was also no difference in systolic or diastolic BP z scores measured when awake between the groups or between the proportion of children who were normotensive, prehypertensive or hypertensive.

Sleep and respiratory characteristics are compared between the groups in Table 2. There was no difference between groups for total sleep time, sleep latency or sleep efficiency. Wake after sleep onset was greater in the children with DS compared to the TD− group ($p < 0.05$). There was no difference in the % time spent in NREM or REM sleep between groups; however, the DS group spent longer in N2 compared to the TD+ group ($p < 0.01$).

By design, there was no difference in OAHI between the DS and TD+ groups and both measures were significantly higher compared to the TD− group ($p < 0.001$ for both). Due to their relationship with the frequency of obstructive events, differences were also evident between both the DS and TD+ groups, and the TD− group for total respiratory disturbance index (RDI), REM RDI, Arousal Index and measures of desaturation. REM RDI was also elevated in the DS groups compared to the TD+ group. In addition, the SpO$_2$ nadir, average SpO$_2$ drop and SpO$_2$ > 4% drop were larger in the DS group compared to the TD+ group ($p < 0.05$ for all). The CnAHI was not different between the DS and TD+ groups, but was higher in the DS group compared to the TD− group ($p < 0.05$). Average transcutaneous CO$_2$ was not different between groups. Periodic leg movements were low in all groups but were statistically higher in the TD− group compared to the DS group.

One child with DS had to be excluded from HRV analysis due to excessive ECG artifact.

Frequency domain HRV measurements are presented in Fig. 1a for HR, Fig. 1b for LF power, Fig. 1c for HF power, Fig. 1d for total power and Fig. 1e for LF/HF during wake before sleep onset, total sleep, N2, N3 and REM sleep. HR was higher in the children with DS compared to both the TD+ children in N2 and N3 and compared to the TD− children during total sleep, N2, N3 and REM sleep. During wake the TD+ children had significantly higher HR compared to both the DS and TD− groups. There were no group differences in LF power (Fig. 1b) in any of the stages. HF power (Fig. 1c) was lower in the DS group compared to the TD+ group in total sleep ($p < 0.01$), N2 ($p < 0.01$) and N3 ($p < 0.05$) sleep. HF power was also lower in the DS group compared to TD− in wake ($p < 0.05$), total sleep ($p < 0.01$), N2 ($p < 0.01$) and N3 ($p < 0.05$). TP (Fig. 1d) was lower in the DS group compared to both TD+ and TD− for total sleep and N2 sleep. LF/HF (Fig. 1e) was higher in the DS group compared to TD+ in wake ($p < 0.01$), total sleep ($p < 0.001$), N2 ($p < 0.001$), N3 ($p < 0.001$) and REM ($p < 0.001$). LF/HF was also higher in the DS group compared to TD− for wake ($p < 0.01$), total sleep ($p < 0.001$), N2 ($p < 0.001$) and N3 ($p < 0.001$). LF/HF was lower in the TD+ group compared to the TD− group in REM sleep.

The effects of sleep state on HRV are presented in Table 3. There were no effects of sleep state on HR in the children with DS. HR was lower in all sleep states compared to wake in both the TD+ and TD− groups. There were no effects of sleep state on LF power in any of the three groups. HF power was not affected by sleep state in the DS or TD− groups. HF power was higher in all sleep states compared to wake in the TD+ group. Total power was not affected by sleep state in the DS or TD− groups; however, TP was lower in wake compared to total sleep, N2 and REM sleep in the TD+ group. LF/HF was higher during wake compared to total sleep, N2 and N3 in the DS group. In the TD+ group LF/HF was also higher during wake compared to all sleep states and LF/HF in REM was also higher compared to total sleep, N2 and N3 sleep. In the TD− group LF/HF was also higher during wake compared to total sleep, N2 and N3 sleep and higher in REM compared to total sleep, N2 and N3 sleep.

In the DS group there were moderately strong positive correlations between OAHI and LF in N2 ($r = 0.499$, $p < 0.001$) and LF/HF in REM ($r = 0.485$, $p < 0.001$) and in the TD+ group between OAHI and LF/HF in total sleep ($r = 0.307$, $p < 0.05$) and N2 ($r = 0.370$, $p < 0.01$).

DISCUSSION

This is the first study to specifically examine heart rate control in children with DS and SDB. We found that compared to TD children matched for age, sex and SDB severity, children with DS had lower HF power, a measure of parasympathetic activity, and higher LF/HF, representing increased sympathovagal balance. In addition, children with DS had higher HR during sleep and the usual fall in

Table 1. Demographic characteristics of the Down syndrome (DS), typically developing children with sleep disordered breathing (TD+) and without sleep disordered breathing (TD−).

	DS	TD+	TD−
n	44	44	44
Sex	25F/19M	23F/21M	24F/20M
Age (years)	8.4 (5.28, 12.8)	7.6 (5.2, 11.1)	8.0 (6.0,11.4)
Height (cm)	123.6 (104.4, 136.0)	124.5 (114.0, 148.0)	130.5[†] (119.4, 148.9)
Weight (kg)	27.3 (17.9, 50.0)	25.2 (20.2, 51.2)	27.4 (22.4, 42.4)
BMI z score	0.94 (0.42, 1.81)	0.85 (0.1, 1.6)	0.4[††] (−0.1, 0.8)
% Obese	31.8[†]	22.7[‡]	6.8
% Overweight	9.0	18.2[‡]	9.0
Neck circumference (cm)	30.0 (27.1, 36.2)	28.0 (26.6, 33.8)	28.0 (26.1, 30.4)
Waist circumference (cm)	62.3 (55.0, 78.5)	60.0 (57.0, 80.0)	59.0 (55.0, 64.8)
Hip circumference (cm)	68.0 (55.0, 78.5)	65.5 (59.3, 89.0)	67.0 (61.0, 78.8)
Systolic BP z score	0.9 (0.3, 1.5)	1.2 (0.6, 1.7)	1.1 (0.4, 1.5)
Diastolic BP z score	0.3 (−0.3, 1.1)	0.7 (0.1, 1.1)	0.5 (0.2, 0.8)
Normotensive (%)	57.1	52.0	56.8
Prehypertensive (%)	14.3	21.0	18.2
Hypertensive (%)	28.6	27.0	25.0

Data presented as median (first, third quartiles).
[†]$p < 0.05$, [††]$p < 0.01$ DS vs TD−.
[‡]$p < 0.05$, TD+ vs TD−.

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Table 2. Sleep and respiratory characteristics of the Down syndrome (DS), typically developing children with sleep disordered breathing (TD+) and without sleep disordered breathing (TD−).

	DS	TD+	TD−
n	44	44	44
Total sleep time (min)	431 (382, 470)	424 (392, 465)	434 (399, 467)
Sleep latency (min)	17.8 (9.0, 47.6)	22.8 (15.1, 46.6)	24.5 (8.8, 45.6)
Wake after sleep onset (%)	10.5 (5.3, 18.6)	6.5 (4.0, 14.0)	6.5[†] (4.0, 11.0)
Sleep efficiency (%)	81.9 (76.3, 90.6)	86.0 (79.1, 90.4)	85.9 (82.2, 92.1)
NREM (%)	82.0 (77.7, 88.5)	81.0 (79.5, 83.1)	81.2 (77.2, 83.8)
N1 (%)	6.1 (2.7, 9.4)	6.9 (4.8, 9.4)	6.3 (5.1, 8.5)
N2 (%)	50.5 (44.3, 55.9)	44.8[**] (41.0, 47.2)	48.8 (41.3, 52.7)
N3 (%)	25.4 (19.9, 33.7)	28.8 (24.4, 31.4)	26.5 (20.7, 29.5)
REM (%)	18.0 (11.5, 22.3)	19.1 (16.9, 20.5)	18.9 (16.3, 22.8)
OAHI (events/h)	4.2 (1.0, 12.7)	4.2[‡‡‡] (1.0, 11.8)	0.2[†††] (0.0, 0.4)
RDI (events/h)	8.0 (3.2, 14.8)	5.9[‡‡‡] (2.0, 14.2)	1.4[†††] (0.8, 2.2)
REM RDI (events/h)	17.0 (5.9, 28.6)	5.5[‡‡‡,**] (2.6, 14.1)	2.1[†††] (0.7, 2.8)
CnAHI (events/h)	1.6 (0.9, 3.2)	1.0 (0.6, 2.2)	0.8[†] (0.4, 1.6)
Arousal Index (events/h)	13.9 (11.2, 18.0)	12.8[‡‡‡] (10.5, 19.9)	10.6[†††] (9.3, 11.4)
SpO$_2$ nadir (%)	88.0 (86.0, 90.0)	91.0[‡,**] (87.3, 94.0)	93.0[†††] (91.0, 94.0)
Average SpO$_2$ drop	4.0 (3.0, 5.0)	3.0[*] (3.0, 4.0)	3.0[†] (3.0, 4.0)
ODI90% (events/h)	0.1 (0.0, 0.5)	0.0[*] (0.0, 0.1)	0.0[†††] (0.0, 0.0)
ODI4% (events/h)	2.5 (1.4, 6.2)	1.0[‡‡,*] (0.4, 3.4)	0.4[†††] (0.1, 0.9)
Av TcCO$_2$ (mmHg)	45.7 (41.1, 48.5)	43.1 (41.0, 47.4)	44.2 (40.3, 48.9)
PLM (Events/hour)	0.0 (0.0, 0.5)	0.0 (0.0, 1.3)	0.7[†] (0.0, 1.4)

Data presented as median (first, third quartiles).
OAHI obstructive apnea hypopnea index, *RDI* respiratory disturbance index, *REM RDI* rapid eye movement respiratory disturbance index, *CnAHI* central apnea hypopnea index, *ODI* oxygen desaturation index, *Av TcCO$_2$* average transcutaneous carbon dioxide, *PLM* periodic leg movements.
*$p < 0.05$, **$p < 0.01$ DS vs TD+.
†$p < 0.05$, †††$p < 0.001$ DS vs TD−.
‡$p < 0.05$, ‡‡$p < 0.01$, ‡‡‡$p < 0.001$ TD+ vs TD−.

heart rate from wake to sleep was not seen. Furthermore, children with DS exhibited greater oxygen desaturation during the night. The combination of impaired heart rate control, lack of nocturnal dipping of heart rate and increased exposure to hypoxia suggests that children with DS are more severely affected by SDB, than are TD children.

We have previously shown that HRV is reduced in TD elementary-school-aged children with SDB compared to non-snoring control children.[29] Our finding that HF power and TP are significantly reduced in children with DS compared to age, sex and SDB severity matched TD children suggests that SDB in these children has an even greater effect on cardiovascular control. Consistent with our previous studies, HF power and TP were also lower in the DS children than in non-snoring TD children. In this study we did not further group the TD children with SDB, based on the severity of their SDB as we had done previously.[29] This was because of our smaller sample size. This may explain why the TD+ children had elevated HF and TP compared to the TD− children, although this did not reach statistical significance. In pre-school TD children we have previously reported elevated HF power in those with moderate/severe OSA.[30] In that study we suggested that this may be explained by increased work of breathing and greater intrathoracic pressure swings in these children as changes in HF are attributed to the effect of respiration.[30] We have previously shown that SDB in TD children is associated with elevated heart rate and blood pressure[32] and impaired control of both heart rate[29] and blood pressure[33] regardless of severity, and these findings are supported by other studies.[18] Further studies are required in children with DS to identify if blood pressure is also affected in children with DS.

The majority of studies that have investigated HRV in individuals with DS have done so during wakefulness in adult populations in order to examine the response to, or recovery from, isometric or dynamic exercise, and have not considered SDB status (for review see ref.[34]). A meta-analysis showed no difference in HRV parameters at rest, except in RMSSD, a measure of parasympathetic activity closely correlated to HF power, which was lower in DS compared to control groups.[34] However, the majority of studies have identified blunted heart rate responses in DS during exercise or autonomic tasks.[35–39] To our knowledge, there has been only one study that has assessed HRV during sleep in children with DS and SDB. In that small study of seven children (aged 8–18 years) with DS, five with SDB, and six TD control children without SDB, 10 min of wake/N1, N2 and slow wave sleep (equivalent to N3) were analyzed during the first or second sleep cycle. The results of this study and the current study are difficult to compare because of the different methods of analysis used. In contrast to our study, Ferri et al. identified increased LF power, indicating increased sympathetic activity. However, our findings of reduced HF power (vagal activity) and increased LF/HF ratio are consistent with that of Ferri et al.[21] Reduced HF power has also been reported in children with DS without respiratory disorders who were studied while awake.[40] Changes in HF are attributed to the effect of respiration, as heart rate accelerates during inspiration and slows during expiration.[23] A lower HF power could suggest that children with DS have a reduced parasympathetic response to blood pressure swings related to respiration. In support of this, we have previously shown that the heart rate responses to both spontaneous arousal from sleep and in response to obstructive events are depressed in children with DS.[19,20]

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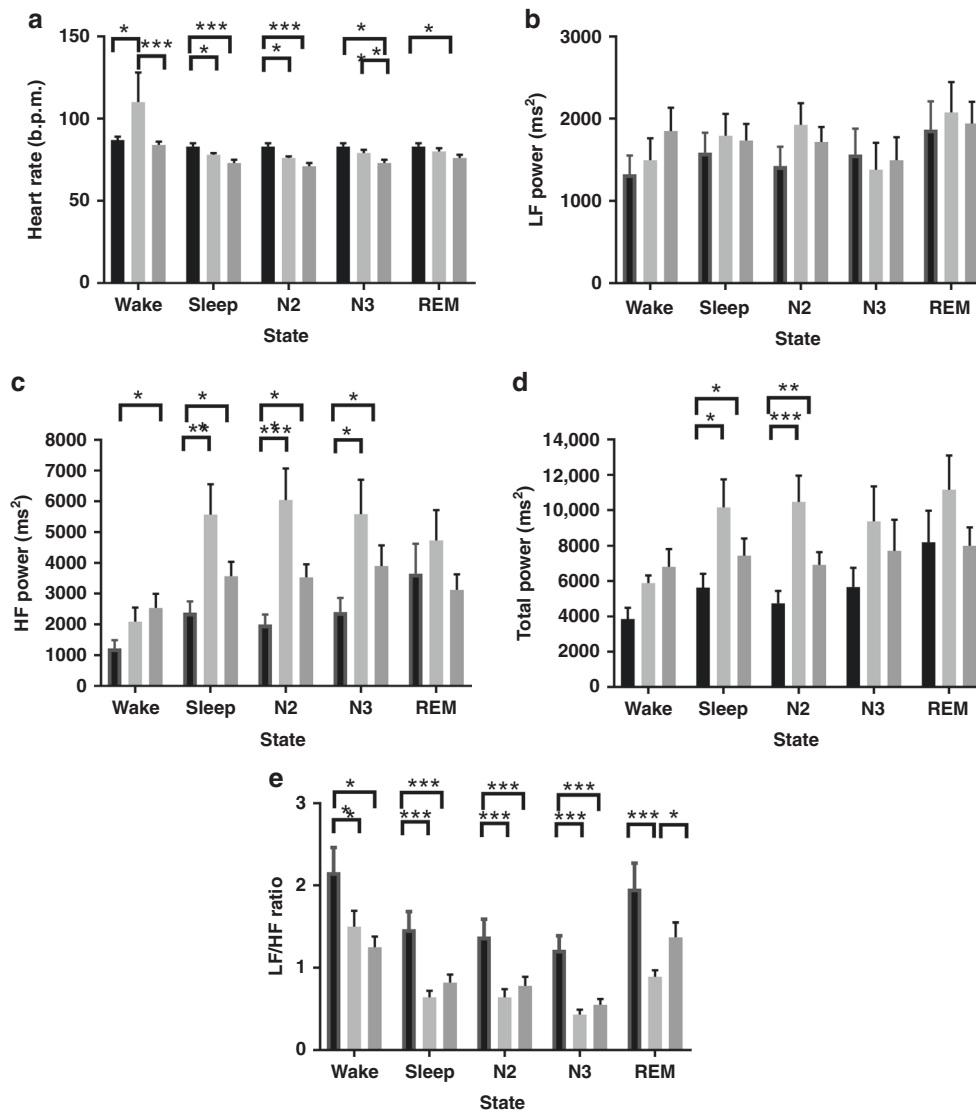
Fig. 1 Heart rate and heart rate variability. Frequency domain heart rate variability in wake before sleep onset, total sleep, N2, N3 and REM sleep in children with Down syndrome (white bars) typically developing children with sleep disordered breathing (light gray bars) and typically developing children without sleep disordered breathing (dark gray bars) for **a** heart rate; **b** LF power; **c** HF power; **d** total power and **e** LF/HF. Values are presented as mean ± SEM as statistical analysis was carried out on normalized values. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

In the current study, LF power was not different between groups. In contrast, previous studies in children with DS have found elevated LF power compared to TD children.[21,40] The differences in findings are likely due to the small sample size in the study by Ferri et al.,[21] and differences in the severity of SDB in the children with DS, as only 5/7 had SDB with an average obstructive apnea index of 1.4 events/h compared to 4.2 events/h in our study. The group of children with DS studied by de Carvalho et al. excluded children with respiratory disorders and they were studied while awake.[40] In support of our findings of no difference in LF power, a recent meta-analysis of HRV studies in adults also showed no difference in LF power when studies were carried out during rest and that there was significant heterogeneity in the findings between studies,[34] as was also observed between individuals in our study. LF power is attributed to both sympathetic and parasympathetic activity, and blood pressure regulation via the baroreceptors. We have previously shown that catecholamine levels (adrenaline, noradrenaline and dopamine) as measures of overall sympathetic activation were significantly reduced in children with DS with SDB compared to TD children

matched for SDB severity.[20] A decrease in overall sympathetic activation indicated by decreased catecholamine levels,[20] and the increased LF/HF in the children with DS as identified in the current study, cannot be extrapolated to surmise the direction of the change in sympathetic cardiac activity.

In the current study we identified that heart rate was elevated during N2 and N3 in the children with DS compared to both TD+ and TD− children. We also did not observe the usual fall in heart rate from wake to sleep in the children with DS. This may indicate that nocturnal dipping, which is widely believed to be restorative to the cardiovascular system, is impaired in these children. This is important, as previously we have shown that nocturnal dipping is preserved in TD children with SDB.[41,42] We also did not observe the elevated HF and total power that we found in the TD+ children during sleep compared to awake, with no effects of sleep state observed, further suggesting autonomic dysfunction in these children. Our findings of lower SpO2 are in keeping with previous studies by our group that identified that when matched for SDB severity, children with DS had worse gas exchange reflected in worse desaturation and higher average pCO2 during sleep.[11]

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Table 3. Effects of sleep state on heart rate variability measurements of the Down syndrome (DS), typically developing children with sleep disordered breathing (TD+) and without sleep disordered breathing (TD−).

	Wake	Sleep	N2	N3	REM
Heart rate					
DS	87 ± 2	83 ± 2	83 ± 2	83 ± 2	83 ± 2
TD+	110 ± 18	78 ± 1***	76 ± 1***	79 ± 2***	80 ± 2***
TD−	84 ± 2	73 ± 2***	71 ± 2***	73 ± 2***	76 ± 2*
LF power					
DS	1326 ± 224	1587 ± 242	1423 ± 236	1563 ± 315	1866 ± 345
TD+	1494 ± 266	1791 ± 268	1923 ± 265	1381 ± 324	2077 ± 368
TD−	1848 ± 285	1737 ± 203	1716 ± 183	1494 ± 280	1941 ± 265
HF power					
DS	1221 ± 267	2382 ± 371	1996 ± 326	2402 ± 458	3648 ± 978
TD+	2091 ± 457	5569 ± 987***	6044 ± 1026***	5582 ± 1118**	4731 ± 988**
TD−	2534 ± 464	3573 ± 462	3529 ± 428	3894 ± 674	3123 ± 510
Total power					
DS	3861 ± 630	5629 ± 787	4742 ± 704	5666 ± 1083	8186 ± 1785
TD+	5889 ± 423	10,157 ± 1587*	10,458 ± 1500*	9358 ± 1986	11,149 ± 1946*
TD−	6810 ± 997	7435 ± 936	6907 ± 732	7706 ± 1748	7992 ± 1034
LF/HF					
DS	2.16 ± 0.30	1.47 ± 0.21*	1.38 ± 0.21**	1.22 ± 0.17***	1.96 ± 0.31
TD+	1.50 ± 0.19	0.64 ± 0.08***,††	0.64 ± 0.10***,††	0.43 ± 0.06***,†††	0.89 ± 0.08**
TD−	1.25 ± 0.13	0.82 ± 0.10**,††	0.78 ± 0.11**,†††	0.55 ± 0.07***,†††	1.37 ± 0.18

Data presented as mean ± SEM.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs Wake.
††$p < 0.01$, †††$p < 0.001$ vs REM.

We have also shown that re-oxygenation following an obstructive respiratory event is delayed.[20] The combination of reduced cardiovascular and ventilatory responses likely exacerbate acute hypoxic exposure during obstructive events. In combination with a lowered nadir in SpO_2 during respiratory events, our findings suggest that children with DS are more affected by the same severity of SDB than TD children if severity is defined according to the traditional means in terms of the frequency of obstructive events. We have previously identified that children with DS referred for assessment of SDB had more severe OSA compared to TD children referred to our sleep laboratory, despite similar symptom scores on the OSA-18 and Pediatric Daytime Sleepiness Scale questionnaires.[11] This suggests OSA may go un-investigated and untreated in children with DS.

In the current study we did not find any difference in awake blood pressure or the numbers of children who were prehypertensive, hypertensive or normotensive between groups. Our findings that only 50–60% of children across the three groups were normotensive is surprising. A recent meta-analysis reported 4% of children to be hypertensive and approximately 10% to be prehypertensive.[43] This study did not include children with SDB which has been shown to elevate blood pressure.[32] It is also possible that the number of obese and overweight children included in our study contributed to the elevated readings, as the study by Song et al.[43] demonstrated that the prevalence of hypertension and prehypertension was significantly elevated in these groups. The high number of obese and overweight children in the DS group may also have affected our HRV results as previously we have shown in TD children with SDB that the strongest modifiable factor determining dampened autonomic control is increased central adiposity, as reflected in the waist and hip circumference and the waist-to-height ratio.[44]

We must acknowledge the limitations of our study. Firstly, we had a small sample of 44 children with DS, the severity of SDB was variable within the group, and we did not have any children with DS who did not have SDB. However, the children were carefully matched to TD children both with and without SDB. Secondly, the children in our DS group were all well and had minimal other comorbidities which may have diminished the hypothesized adverse effects on autonomic control. Therefore, we cannot infer what effects SDB might have in children with DS with more significant comorbidities. Thirdly, the relationships we have demonstrated between DS and adverse cardiovascular findings are cross-sectional, and determining the impact of treatment of SDB will be important in confirming the clinical implications of our findings. It must be noted that as is common with HRV analysis, there were often large individual differences in absolute LF and HF power between subjects, which was reflected in the magnitude of individual differences between groups for HF power. Therefore, the significant effect observed in the LF/HF ratio is in part because the ratio eliminates these individual differences in absolute power. Finally, we acknowledge that we did not adjust our statistical approach for multiple testing.

In conclusion, our study has identified that children with DS and SDB have impaired autonomic control of heart rate and an increased exposure to hypoxia compared to matched TD children, suggesting that the adverse effects of SDB are exacerbated. As SDB has significant adverse effects on the cardiovascular system in TD children and children with DS are at significantly increased risk of severe SDB, it is important that these children are screened and treated as early as possible, to optimize their future cardiovascular outcomes.

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AUTHOR CONTRIBUTIONS

R.S.C.H. conceptualized and designed the study, obtained funding, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript. A.S., A.B., J.T. and L.M.W. carried out the initial analyses, and reviewed and revised the manuscript. M.J.D. critically reviewed the manuscript for important intellectual content. G.M.N. conceptualized and designed the study, obtained funding and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ADDITIONAL INFORMATION

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