http://dx.doi.org/10.5665/sleep.3770

Effects of Obstructive Sleep Apnea and Obesity on Exercise Function in Children

Carla A. Evans, BSc(Hons), PhD[1]; Hiran Selvadurai, MBBS, PhD, FRACP[1,2]; Louise A. Baur, MBBS (Hons), BSc(Med), PhD, FRACP[1,3]; Karen A. Waters, MBBS, PhD, FRACP[1,2]

[1]The Children's Hospital at Westmead Clinical School, Discipline of Paediatrics & Child Health, Faculty of Medicine, The University of Sydney NSW Australia; [2]The Department of Respiratory Medicine, The Children's Hospital at Westmead, Westmead NSW Australia; [3]Weight Management Service, The Children's Hospital at Westmead, Westmead NSW Australia

Study Objectives: Evaluate the relative contributions of weight status and obstructive sleep apnea (OSA) to cardiopulmonary exercise responses in children.

Design: Prospective, cross-sectional study. Participants underwent anthropometric measurements, overnight polysomnography, spirometry, cardiopulmonary exercise function testing on a cycle ergometer, and cardiac doppler imaging. OSA was defined as ≥ 1 obstructive apnea or hypopnea per hour of sleep (OAHI). The effect of OSA on exercise function was evaluated after the parameters were corrected for body mass index (BMI) z-scores. Similarly, the effect of obesity on exercise function was examined when the variables were adjusted for OAHI.

Setting: Tertiary pediatric hospital.

Participants: Healthy weight and obese children, aged 7–12 y.

Interventions: N/A.

Measurements and Results: Seventy-one children were studied. In comparison with weight-matched children without OSA, children with OSA had a lower cardiac output, stroke volume index, heart rate, and oxygen consumption (VO_2 peak) at peak exercise capacity. After adjusting for BMI z-score, children with OSA had 1.5 L/min (95% confidence interval -2.3 to -0.6 L/min; P = 0.001) lower cardiac output at peak exercise capacity, but minute ventilation and ventilatory responses to exercise were not affected. Obesity was only associated with physical deconditioning. Cardiac dysfunction was associated with the frequency of respiratory-related arousals, the severity of hypoxia, and heart rate during sleep.

Conclusions: Children with OSA are exercise limited due to a reduced cardiac output and VO_2 peak at peak exercise capacity, independent of their weight status. Comorbid OSA can further decrease exercise performance in obese children.

Keywords: child, exercise function, heart, obesity, obstructive sleep apnea

Citation: Evans CA, Selvadurai H, Baur LA, Waters KA. Effects of obstructive sleep apnea and obesity on exercise function in children. *SLEEP* 2014;37(6):1103-1110.

INTRODUCTION

Growing evidence suggests that a bidirectional relationship exists between childhood obesity and sleep dysfunction. Childhood obesity is a major risk factor for obstructive sleep apnea (OSA), and the likelihood of an obese child developing OSA is four to five times greater than in a nonobese child.[1] Conversely, school-aged children are at risk of developing future obesity if they sleep less than 9 h per night[2] or if they have OSA.[3]

OSA is associated with left ventricular hypertrophy, elevated heart rate (HR), and impaired ventilatory responses to carbon dioxide during sleep. Children with an apnea-hypopnea index (AHI) greater than 10 h^{-1} are at risk of left ventricular hypertrophy and this correlates with AHI and the severity of hypoxia during sleep.[4] Children with OSA have impaired left ventricular diastolic function,[5] but systolic function and left ventricular ejection fraction are maintained.[5-7] HR is elevated during wake and sleep, whereby children with an AHI greater than 5 h^{-1} have a mean HR approximately 5 to 9 bpm higher than nonsnoring or snoring children.[8] This increase in HR is likely a consequence of changes in autonomic function.[9-11] Children with OSA have significantly elevated sympathetic activity at rest[9,12] and blunted sympathetic activity (baroreflex gain) in response to sleep and stress, whereas parasympathetic activity remains unaffected.[11,13] The increase in baseline sympathetic activity correlates with AHI and hypoxia.[12,14] In regard to lung function, pulmonary function is generally unaffected by OSA,[15,16] but children with OSA have impaired ventilatory responses to increased carbon dioxide during sleep[17] but not during quiet wakefulness.[18]

Cardiopulmonary exercise testing (CPET) can be used to assess physical conditioning, and in adults, it can also be used as a prognostic marker.[19] Two variables used to assess future risk of cardiovascular disease and mortality in adults are oxygen consumption and the ventilatory response to carbon dioxide at peak exercise capacity (i.e. VO_2 peak and V_E/VCO_2, respectively).[20-22] In healthy individuals, VO_2 peak is approximately 30 to 50 mL/kg/min and V_E/VCO_2 at peak exercise capacity is approximately 25, but a VO_2 peak less than 14 to 15 mL/kg/min and a V_E/VCO_2 greater than 33 have been shown to be markers of a poor prognosis and future risk of mortality in adults.[19-22] In children, little is known about the longitudinal effect of a low VO_2 peak or high V_E/VCO_2.[23] One study examined exercise function in children with OSA and found that children with OSA achieve peak exercise capacity at a lower workload, HR, and a lower VO_2 peak relative to age and sex.[24] Although estimates of obese children having diagnosed OSA are anywhere from 19–78%[25-29] the outcomes from this study were not adjusted for weight status, nor did they evaluate cardiac output.[24]

Submitted for publication July, 2013
Submitted in final revised form January, 2014
Accepted for publication January, 2014

Address correspondence to: Dr Carla A Evans, Room 206, Blackburn Building D06, The University of Sydney NSW Australia 2006; Tel: +61 2 9351 5165; Fax: +61 2 9845 3396; E-mail: CarlaE@uni.sydney.edu.au

Previous studies have found obese children achieve peak exercise earlier and at a lower workload than healthy weight children.[30,31] This poor exercise function in obese children is thought to be a consequence of physical deconditioning and tiring earlier because of carrying a heavier body mass, but no studies have documented the prevalence of OSA in their sample groups or determined the effect of OSA on exercise function in children.[30-35]

The first aim of this study was to assess cardiopulmonary exercise function in children with OSA. Because obesity is a risk factor for OSA, we than compared the relative contributions of obesity versus OSA to cardiopulmonary function. We hypothesized that children with OSA, irrespective of weight status, are exercise restricted because of an impaired cardiovascular response to stress.

METHODS

This was a cross-sectional, prospective study approved by the Human Research Ethics Committee. The primary caregiver(s) gave written informed consent and the children gave verbal consent. Data collection was performed during a single visit.

Between February 2009 and June 2011, children age 7 to 12 y were recruited from the Sleep Clinic or Weight Management Service at the Children's Hospital at Westmead NSW Australia, and from the community. Community-based children were a convenience sample of children known to the investigators. Children were included if they snored at least "a little of the time" according to the OSA-18 survey,[36] were clinically evaluated to be healthy weight or obese, and were at least 135 cm tall in order to successfully reach the bicycle's pedals and perform the CPET. Using the United States Centers for Disease Control and Prevention (US CDC) guidelines, children were defined as being of healthy weight if their body mass index (BMI) percentile was between the 5th and 85th centiles for age and sex, and obese if their BMI percentile was ≥ 95th for age and sex.[37] Age- and weight-matched, nonsnoring children were also recruited for comparison. To clarify the effect of obesity on exercise function, and for time management purposes, children were excluded from the study if they were overweight (i.e. had a BMI between the 85th and 95th percentile). Children were also excluded if they were developmentally delayed, had an underlying syndrome, received a diagnosis of a sleep disorder other than OSA, or were already established on treatment.

Anthropometry

Height, weight, and waist circumference were measured. Standing height was measured to the nearest 0.1 cm and weight was measured to the closest 0.01 kg. BMI was calculated as weight/height^2 (kg/m^2), and BMI percentiles and z-scores were determined using the US CDC reference values.[37] Waist circumference was measured to the nearest 0.1 cm at the smallest point between the lowest rib and iliac crest. To assess for central obesity, waist-to-height ratio (WHtR) was calculated as waist/height (cm/cm), and central obesity was defined as WHtR > 0.5.[38]

Polysomnography

Overnight polysomnography was performed at the David Read Sleep Unit, at The Children's Hospital at Westmead NSW Australia, in accordance with the 1997 American Thoracic Society (ATS) guidelines[39] using the Sandman Elite® Version 9.2 system (Embla Systems, Broomfield, CO, USA). Data collection commenced between 19:30 and 21:00, and ended at 06:00.

Data analysis was performed in accordance with the 2007 American Academy of Sleep Medicine guidelines.[40] Sleep stages and arousals were determined according to central and occipital electroencephalogram (EEG), a left and right electrooculogram (EOG) and submental electromyogram (EMG) signals. Nasal airflow was measured using nasal cannula. Nasal and oral airflow was also monitored using a thermistor, respiratory effort was monitored using diaphragmatic and abdominal surface electrode EMG and chest and abdominal plethysmography, and ventilation was monitored using oximetry (SpO_2) and transcutaneous carbon dioxide ($TcCO_2$) monitoring. Respiratory events were scored if they were at least two respiratory cycles long, and significant oxygen desaturations were defined as ≥ 3% desaturation from baseline. An obstructive apnea-hypopnea index (OAHI) ≥ 1 h^{-1} was used as a diagnosis for OSA.[41]

To assess sleepiness among children with and without OSA, the modified Epworth Sleepiness Scale (ESS) questionnaire was completed by the child at the time of the polysomnography.[42] The results were analyzed according to set criteria.[43]

Spirometry

Spirometry was performed according to ATS guidelines[44] against predicted values for race, age, sex, and height[45] using the Medgraphics CPX/D breath-by-breath exchange system (Medgraphics Corporation, St Paul, MN, USA) and BreezeSuite Version 6.4.1 software program (Medgraphics Corporation), or Vmax Encore 229 equipment (CareFusion, San Diego, CA, USA) and Vmax Series Version 21-1A software (CareFusion). Results are displayed as absolute (L) and as percent predicted values for race, age, sex, and height.[45]

Doppler

Cardiac output (L/min), cardiac output index (QI; L/min/m^2), stroke volume (SV; mL), stroke volume index (SVI; mL/m^2), and HR (bpm) were recorded at rest and at peak exercise, in an upright position using an Ultrasonic Cardiac Output Monitor (USCOM) Doppler, Version 1.8.0.0 (USCOM, Sydney, NSW, Australia).[46] Cardiac index and SVI were calculated by adjusting cardiac output and stroke volume for body surface area.[47]

Cardiopulmonary Exercise Testing

Prior to the CPET, the caregiver(s) reported the number of hours of physical/sporting activity the child did each week. CPET was performed and analyzed in accordance with ATS and American College of Chest Physicians (ACCP) guidelines[19] using a cycle ergometer (Excalibur Sport cycle ergometer, the Medgraphics CPX/D Breath-by-Breath Exchange system and BreezeSuite Version 6.4.1 software program, Medgraphics Corporation). Children cycled at 60 revolutions per min (rpm) against increasing resistance (10 watts/min). Tests were terminated when (1) the child felt physically exhausted and could not maintain a speed of 60 rpm despite encouragement, or (2) if the child reached their predicted maximal HR (i.e., maximal

HR = 220 – age). The test was deemed satisfactory if the respiratory quotient (RQ) was greater than 1.00; however, the child was encouraged to continue with the test as long as possible (i.e. RQ ≥ 1.05) to ensure true peak exercise capacity was achieved. Exercise data from any child considered not to achieve peak exercise capacity was excluded from the analysis. Physical exhaustion was recorded using the Borg scale,[48] a subjective scale validated in children.[49,50] Output was averaged at 30-sec intervals and compared with reference values.[51]

Statistical Analysis

Statistical analysis was performed using SPSS version 19 (SPSS, Chicago, IL, USA). Categorical variables are described as frequencies and compared between groups using the chi-square test. Continuous variables were checked for normality and corrected if required.[52] Descriptive data are reported as mean (standard deviation [SD]) and compared using independent *t*-tests.

Analysis of covariance was used to evaluate effects of weight status by adjusting for OAHI, and to evaluate effects of OSA by adjusting for BMI z-score with results presented as estimated mean (standard error [SE]), mean difference, and 95% confidence intervals (CIs).

Pearson correlation coefficient analysis was used to assess correlations between sleep, and anthropometric and cardiopulmonary variables. Stepwise multiple regression analysis was performed to develop models that predicted cardiopulmonary function while accounting for any interactions amongst variables. $P < 0.05$ was considered significant.

RESULTS

Of 115 children approached to participate in the study, 71 families consented and the children met the inclusion criteria. These 71 children (mean age 10 ± 1.6 y) included 29 (41%) healthy weight and 42 (59%) obese children. Patient demographics and polysomnography results are detailed in Table 1. Forty children had OSA, including 10 healthy weight and 30 obese children. Children with OSA had significantly more arousals, oxygen desaturations, lower nadir SpO_2, and higher sleeping HR than children without OSA. There was no difference in the percentage of time spent in each sleep stage (results not shown), or ESS scores between those with and without OSA.

Cardiopulmonary Exercise Function in Children With and Without OSA

As shown in Tables 2 and 3, children with OSA had significantly lower RQ, HR, SVI, Q, and VO_2 peak at peak exercise capacity and a non-significant trend for children with OSA to achieve peak exercise capacity at a lower workload than those without OSA ($P = 0.06$). Children with OSA had a higher breathing reserve at peak exercise than those without OSA (i.e. V_E/maximum voluntary ventilation (MVV) 54% and 45%; $P < 0.05$).

Among children with and without OSA, no differences existed for the number of hours of organized exercise per week (Table 2), pulmonary lung function, V_E, gas exchange (results not shown), or Q at rest (4.6 ± 1.2 L/min versus 4.5 ± 1.1 L/min, not significant).

Table 1—Subject demographics and polysomnography results

Variable	No OSA	OSA	P value
n	31	40	
Sex (m:f)	11:20	27:13	0.81
Age (y)	10.2 (1.6)	10.1 (1.6)	0.85
Height (m)	144.5 (11.4)	145.8 (10.4)	0.61
Weight (kg)	46.50 (21.25)	57.67 (21.12)	0.03
BMI (kg/m^2)	21.5 (7.1)	27.0 (8.4)	0.005
BMI z-score	0.67 (1.47)	1.61 (1.48)	0.009
WC (cm)	74.9 (19.5)	88.9 (21.9)	0.01
WHtR	0.52 (0.12)	0.61 (0.13)	0.01
Habitual snorers (y:n)	17:13	31:4	0.005
Sleep latency (min)	22.6 (13.2)	34.5 (28.1)	0.02
Sleep efficiency (%)	85.3 (8.8)	81.4 (10.4)	0.10
AHI (h^{-1})	1.5 (1.1)	11.5 (10.5)	< 0.001
OAHI (h^{-1})	0.4 (0.3)	8.9 (10.0)	< 0.001
AI (h^{-1})	6.5 (2.5)	12.2 (8.2)	< 0.001
RAI (h^{-1})	0.8 (0.8)	6.3 (6.8)	< 0.001
Baseline SpO_2 (%)	98 (1)	98 (2)	0.18
Nadir SpO_2 (%)			
TST	90 (4)	85 (9)	0.002
NREM	91 (3)	87 (6)	< 0.001
REM	93 (2)	88 (10)	0.002
ODI (h^{-1})			
TST	2.2 (1.6)	8.6 (8.7)	< 0.001
NREM	1.9 (1.4)	6.3 (5.4)	< 0.001
REM	3.0 (2.4)	20.4 (32.2)	0.002
Baseline $TcCO_2$ (mmHg)	41 (3)	41 (4)	0.90
Peak $TcCO_2$ (mmHg)			
NREM	47 (4)	50 (5)	0.05
REM	46 (5)	48 (5)	0.15
Heart rate (bpm)			
Baseline	83 (10)	88 (12)	0.06
TST	73 (9)	80 (12)	0.008
NREM	73 (9)	79 (11)	0.009
REM	74 (10)	80 (10)	0.01
ESS	5.5 (2.9)	6.5 (4.4)	0.19

Results are presented as means (standard deviation) and frequencies for groups. P values were obtained from chi-square or independent *t*-test analysis. $P < 0.05$ was considered significant. OSA, obstructive sleep apnea; BMI, body mass index; WC, waist circumference; WHtR,waist-to-height ratio; sleep latency, time taken for sleep onset to occur after lights out; Sleep efficiency, percentage of time spent asleep after lights out; reported habitual snoring, snoring at least "a little of the time," as reported by the primary caregiver using the OSA-18 survey,[36] AHI, apnea-hypopnea index; OAHI, obstructive apnea-hypopnea index; CAHI, central apnea-hypopnea index; AI, arousal index; RAI, respiratory arousal index; SpO_2, pulse oximetry; baseline, measured during quiet wakefulness; TST, total sleep time; NREM, non-rapid eye movement; REM, rapid eye movement; ODI, oxygen desaturation index: an oxygen desaturation was defined as a SpO_2 desaturation ≥ 3% from baseline; $TcCO_2$, transcutaneous carbon dioxide; ESS, modified Epworth Sleepiness Scale.[42]

The decrease in Q at peak exercise capacity was caused by both a lower peak HR and SVI. The HR for children with OSA

Table 2—Cardiopulmonary function for children with and without obstructive sleep apnea

Variable	No OSA (n = 29)	OSA (n = 39)	P value
FVC (L)	2.46 (0.60)	2.57 (0.67)	0.45
FVC (%)	98 (10)	98 (12)	0.96
FEV_1 (L)	2.05 (0.46)	2.19 (0.55)	0.28
FEV_1 (%)	91 (11)	91 (14)	0.89
FEV_1/FVC (%)	85 (8)	85 (5)	0.62
Reported exercise (h/w)	3.3 (2.5)	2.0 (2.8)	0.11
Peak work (watts)	83 (22)	69 (31)	0.06
Borg scale	8 (1)	8 (1)	0.18
RQ	1.09 (0.09)	1.04 (0.06)	0.02
V_E/VO_2	32 (4)	32 (5)	0.53
V_E/VCO_2	30 (3)	30 (5)	0.58
V_E peak (L/min)	39.06 (11.67)	34.73 (10.48)	0.14
VO_2 peak (L/min)	1.20 (0.35)	1.14 (0.41)	0.59
VO_2 peak (mL/kg/min)	29.65 (9.21)	20.82 (8.28)	< 0.001
VCO_2 (L/min)	1.24 (0.38)	1.19 (0.44)	0.61
V_E/MVV	0.55 (0.18)	0.46 (0.13)	0.03
SpO_2 (%)	96 (3)	96 (4)	0.59
VO_2/HR (mL)	7.02 (2.19)	7.09 (2.47)	0.91

All unadjusted data are expressed as mean (standard deviation). P values were obtained from independent *t*-test analysis. P < 0.05 was considered significant. OSA, obstructive sleep apnea; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second. Percent predicted values were calculated from Wang et al.[45]; reported exercise = number of hours of organized sport outside of school per week, as reported by the primary carer; Borg scale, a subjective measure of work intensity at peak exercise capacity, as reported by the participant,[48] RQ, respiratory quotient; RQ, = VCO_2:VO_2; V_E/VO_2, the ventilatory equivalent for oxygen; V_E/VCO_2, the ventilatory equivalent for carbon dioxide; V_T, tidal volume; RR, respiratory rate; V_E peak, minute ventilation at peak exercise capacity; VO_2 peak, oxygen consumption at peak exercise capacity; VCO_2, expired carbon dioxide; MVV, maximum voluntary ventilation: MVV = $FEV_1 \times 35$ [70]; V_E/MVV, dyspnea index; SpO_2, pulse oximetry; VO_2/HR, oxygen pulse, amount of oxygen in the blood per heartbeat. n = number of participants involved in analysis.

increased by 66 ± 20 bpm in response to exercise, to achieve a peak HR of 159 ± 18 bpm. In children without OSA, HR increased by 87 ± 24 bpm from rest (P < 0.001) to reach a peak HR of 173 ± 21 bpm (P < 0.05). SVI was significantly lower at rest and peak exercise for children with versus without OSA; SVI at rest was 33.5 ± 9.1 mL versus 41.1 ± 7.2 mL (P < 0.001), and at peak exercise it was 37.8 ± 10.1 mL versus 48.2 ± 9.6 mL (P < 0.001). There was no difference in V_E or ventilatory responses at peak exercise between the two groups.

Effects of Obesity Versus OSA on Cardiopulmonary Exercise Function

Effects of OSA versus obesity on cardiopulmonary function are summarized in Table 4. When corrected for BMI z-score, children with OSA still had cardiovascular dysfunction during exercise, with a significantly lower V_E/MVV, HR, SVI, Q, QI and VO_2 peak than children without OSA. When corrected for BMI z-score, Q at peak exercise capacity in children with

Table 3—Cardiac output at peak exercise capacity for children with and without obstructive sleep apnea

Variable	No OSA (n = 28)	OSA (n = 39)	P value
Q (L/min)	10.5 (1.3)	8.9 (1.5)	< 0.001
QI (L/min/m^2)	8.3 (1.9)	6.0 (1.8)	< 0.001
SV (mL)	61.7 (9.8)	56 (8)	0.06
SVI (mL/m^2)	48.2 (9.6)	37.8 (10.1)	< 0.001
HR (bpm)	173 (21)	159 (18)	0.006

OSA, obstructive sleep apnea; Q, cardiac output; QI, cardiac index; SV, stroke volume; SVI, stroke volume index; HR, heart rate; n, number of participants involved in analysis. All unadjusted data are expressed as mean (standard deviation). P values were obtained from independent *t*-test analysis. P < 0.05 was considered significant.

and without OSA was 9.0 ± 0.2 L/min and 10.4 ± 0.3 L/min (P = 0.001). This impaired Q at peak exercise was associated with a SVI 4.5 mL lower (95% CI -8.2 to -0.8 mL; P < 0.05) and a HR response 14.9 bpm less (95% CI -26.2 to -3.6 bpm; P = 0.01) than those without OSA. VO_2 peak for children with and without OSA was 22.22 mL/kg/min and 27.33 mL/kg/min (P = 0.02).

Conversely, when exercise function was corrected for OAHI, obesity was only associated with a deceased RQ and VO_2 peak (Table 4). Differences in VO_2 peak between healthy-weight and obese children were only seen if VO_2 peak was expressed 'per kilogram' (31.31 mL/kg/min and 18.83 mL/kg/min, respectively; P < 0.001). Pulmonary and cardiovascular function was not different between healthy-weight and obese children (results not shown).

Determinants of Exercise Function

Significant correlations among anthropometric, sleep, and cardiopulmonary function variables indicated that exercise function was inversely associated with weight status, central obesity, OSA severity, arousals, intermittent hypoxia, and HR during sleep. Specifically, RQ correlated with BMI z-score and WHtR. HR, SVI, Q, and VO_2 peak at peak exercise capacity correlated with BMI z-score, OAHI, the respiratory arousal index, and hypoxia during sleep (Figure 1). SVI, HR and VO_2 peak at peak exercise capacity also correlated with WHtR, and mean HR during sleep.

After multiple regression modeling (Table 5), OSA severity (i.e., OAHI) was not a strong predictor of cardiac output or exercise function. Instead, physical conditioning was strongly dependent on BMI z-score, and cardiac function was most dependent on BMI z-score, sleep efficiency, the respiratory arousal index, hypoxia, and HR during sleep. The strongest predictor for RQ was BMI z-score. Peak cardiac output was most dependent on the respiratory arousal index. The strongest model to predict cardiac output's response from rest to exercise included BMI z-score and mean HR during total sleep time. The strongest model to predict SVI at peak exercise included BMI z-score and sleep efficiency. The strongest model to predict HR at peak exercise capacity included nadir SpO_2 in non-rapid eye movement (NREM) sleep. The strongest model to predict HR

Table 4—Cardiopulmonary function at peak exercise capacity between groups: A: healthy weight versus obese (adjusted for obstructive apnea-hypopnea index) or B: obstructive sleep apnea versus non obstructive sleep apnea (adjusted for body mass index z-score).

	A			B		
Variable	Healthy weight (n = 27)	Obese (n = 35)	P value	No OSA (n = 24)	OSA (n = 38)	P value
RQ	1.09 (0.02)	1.03 (0.01)	0.003	1.07 (0.02)	1.05 (0.01)	0.20
VE/MVV	0.49 (0.03)	0.50 (0.03)	0.91	0.56 (0.03)	0.45 (0.03)	0.04
Q (L/min)	9.9 (0.3)	9.3 (0.3)	0.18	10.4 (0.3)	9.0 (0.2)	0.001
QI (L/min/m^2)	8.6 (0.3)	5.5 (0.2)	< 0.001	7.6 (0.3)	6.4 (0.2)	0.001
SVI (mL/m^2)	51.2 (1.5)	34.7 (1.3)	< 0.001	44.6 (1.4)	40.1 (1.1)	0.02
HR (bpm)	169 (4)	161 (3)	0.15	171 (4)	160 (3)	0.05
VO_2peak (L/min)	1.09 (0.08)	1.22 (0.07)	0.20	1.30 (0.08)	1.14 (0.07)	0.13
VO_2peak (mL/kg/min)	31.31 (1.44)	18.83 (1.23)	< 0.001	27.33 (1.58)	22.22 (1.21)	0.02

Analysis of covariance was performed. Only significant results are shown. Nonsignificant results are not shown. Analysis of obesity effects on cardiopulmonary exercise variables were corrected for obstructive apnea-hypopnea index. Analysis of OSA effects was corrected for BMI z-score. Data are expressed as estimated mean (standard error). P values were obtained from analysis of covariance between obese versus healthy weight groups, or OSA versus no OSA groups. P < 0.05 was considered significant. OSA, obstructive sleep apnea; RQ, respiratory quotient; RQ, VCO_2:VO_2; V_E, minute ventilation; MVV, maximum voluntary ventilation, MVV = $FEV_1 \times 35^{70}$; V_E/MVV, dyspnea index; Q, cardiac output; QI, cardiac index; SVI, stroke volume index; HR, heart rate; VO_2peak, oxygen consumption at peak exercise capacity; n = number of participants involved in analysis.

response from rest to peak exercise included BMI z-score and mean HR during REM sleep. The strongest model for VO_2peak included WHtR and the HR response to exercise.

DISCUSSION

This study is the first to assess the relative contributions of OSA and obesity to exercise function in children. Regardless of weight status, OSA was independently associated with exercise dysfunction in children, and this was attributable to cardiovascular dysfunction. Specifically, at peak exercise capacity, children with OSA have a lower HR, stroke volume index, cardiac output, and VO_2peak than those without OSA. Furthermore, obesity and OSA had compounded effects on exercise capacity, more than either obesity or OSA alone.

The Effect of OSA on Cardiopulmonary Function During Exercise

The most significant outcome from this study was that cardiac output at peak exercise is affected by the presence of OSA in children. No equivalent data exist in children, but research in adults have demonstrated impaired cardiovascular performance is linked to OSA, although the mechanism remains debated, with possibilities including lower stroke volume at peak exercise[53] and lower peak HR.[54,55] Przybylowski et al. reported peak HR was not significantly different between patients with mild to moderate or severe OSA,[56] but our subject numbers did not allow this analysis. Of interest, the HR characteristics we found in children are similar to the pattern of change seen in adult patients with heart failure where HR at baseline is equivalent but at peak exercise capacity it is significantly lower for those with chronic heart failure compared with healthy controls.[21] This pattern suggests a significant role of the sympathetic nervous system.

There was an independent effect of OSA on VO_2peak. The magnitude of reduction in VO_2peak in children with OSA is similar to that seen in children with congenital heart disease compared with age- and sex-matched controls.[57] Results from

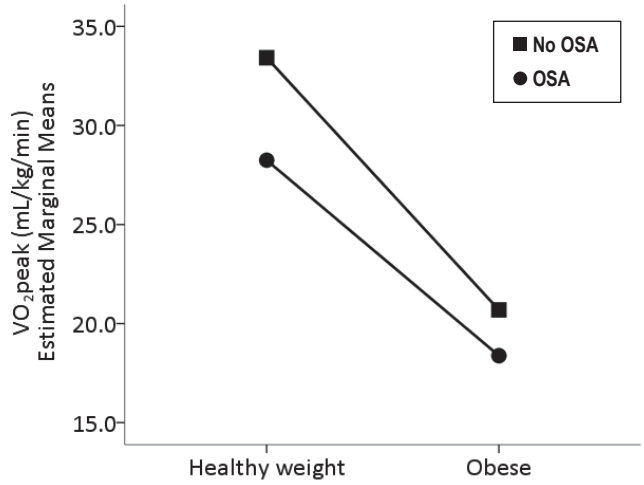

Figure 1—The effect of obesity and obstructive sleep apnea (OSA) on oxygen consumption at peak exercise capacity (VO_2peak). The results are displayed as estimated marginal means. Covariates appearing in the model are evaluated at the following values: Obstructive apnea-hypopnea index = 8.9 h^{-1} and body mass index z-score = 1.14.

adult studies vary, with some showing no differences,[53,54] whereas others report that OSA is associated with lower VO_2peak in a dose-dependent manner.[55,56,58] Results from Lin et al. is consistent with our study results, whereby they reported adults with OSA had a mean VO_2peak of 21.64 mL/kg/min compared to 30.10 mL/kg/min for those without OSA.[59]

V_E/MVV is a ratio used to describe how much breathing reserve an individual has when peak exercise capacity is achieved. For example, a V_E/MVV of 0.70 indicates that the individual has used 70% of his or her breathing capacity at peak exercise (and they have 30% in reserve). We found that children with OSA had a lower V_E/MVV, and thus a greater breathing reserve at peak exercise capacity than those without

Table 5—Regression models involving anthropometric and sleep variables to predict cardiopulmonary function.

Variable	Equation	R^2
RQ	1.078 – (0.021 × BMI z-score)	0.151
SVIpeak (mL/m^2)	26.331 – (5.464 × BMI z-score) + (0.262 × sleep efficiency)	0.685
HRpeak (bpm)	76.786 + (0.991 × nadir SpO_2 in NREM)	0.118
HRchange (bpm)	147.457 – (6.121 × BMI z-score) – (0.862 × HR in REM)	0.322
Qpeak (L/min)	9.893 – (0.091 × respiratory arousal index)	0.145
Qchange (L/min)	9.806 – (0.501 × BMI z-score) – (0.058 × HR during TST)	0.324
VO_2peak (mL/kg/min)	40.247 – (44.205 × WHtR) + (0.130 × ΔHR)	0.524
VO_2peak (L/min)	0.230 + (0.097 × BMI z-score) + (0.090 × Qpeak)	0.190

RQ, respiratory quotient at peak exercise capacity, RQ = VCO_2:VO_2; BMI, body mass index; SVIpeak, stroke volume index at peak exercise capacity; HRpeak, heart rate at peak exercise capacity; SpO_2, pulse oximetry; NREM, nonrapid eye movement sleep; HRchange, change in heart rate from rest to peak exercise capacity; HR, heart rate; REM, rapid eye movement; Qpeak, cardiac output at peak exercise capacity; Qchange, change in cardiac output from rest to peak exercise capacity; TST, total sleep time; VO_2peak, oxygen consumption at peak exercise capacity; WHtR, waist to height ratio; ΔHR, change in heart rate from rest to peak exercise capacity.

OSA. This supports the notion that pulmonary function is not a limiting factor for children with OSA, and instead, as our other assessments of cardiac output suggest, the limitations were more likely to be cardiac in nature. The only equivalent studies available were undertaken in adults, in whom results are inconsistent, although some show the same pattern as in children.[54,59]

The difference in exercise function occurred despite equivalent reported hours of organized sport and physical activity per week, and equivalent modified ESS scores in the children with or without OSA. The peak exercise capacity in those with OSA was 14 watts lower than those without OSA (95% CI -28.8 to 0.7 watts, P = 0.06). At peak workload, there was no difference in the respiratory quotient or the degree of perceived exertion between groups; these findings are similar to adult-based studies that report no difference in peak workload[53,54] or the degree of perceived exertion[54] between adults with and without OSA.

The Effect of Obesity on Cardiopulmonary Exercise Function

Obese children achieved peak exercise capacity at a lower respiratory quotient and had a lower VO_2peak (per kilogram), indicating fatigue and physical deconditioning. Rowland et al. also found that obese children ceased exercise at a lower respiratory quotient although the children in their study had higher absolute VO_2peak.[32] Other studies of obese children having low VO_2peak[32] report VO_2peak as per kilogram, which adjusts VO_2peak for total body mass including fat mass and fat-free mass. This allows bias, predisposing obese children to an artificially poorer outcome.[60] Nonetheless, we found that weight status, not OSA, alters physical conditioning. Obese children are predisposed to a higher VO_2peak (i.e. L/min) because they have a larger left ventricle, stroke volume, and thus cardiac output than healthy-weight children.[32] However, correcting VO_2peak for total body mass (i.e. mL/kg/min; fat mass and fat-free mass) can skew aerobic function for obese children as fat mass does not metabolize oxygen.

This study reinforces the concept that physical decondition is associated with obesity and not OSA. Compared with healthy-weight children, obese children had a lower respiratory quotient at peak exercise capacity. In particular, this study showed the respiratory quotient was dependent on BMI z-score and waist-to-height ratio, indicating that physical deconditioning is related to body mass and central obesity. Children with OSA achieved similar respiratory quotients at peak exercise capacity as weight-matched children without OSA.

Giordano et al. found that cardiac output at peak exercise is not affected by obesity[61]; however, when indexed for body surface, cardiac index and stroke volume index were significantly lower in obese compared to healthy weight children. Correcting cardiovascular function for body surface area is common, but doing so obscures the effect of obesity on cardiac output and stroke volume.[62] Our study found obesity does not affect cardiac output at peak exercise capacity.

Correlations and Proposed Mechanisms Between Sleep, Anthropometry, and Exercise Function

The major influences on cardiovascular function and VO_2peak were weight status, central obesity, cortical arousals, hypoxia and mean HR during sleep. VO_2peak (mL/kg/min) is dependent upon the HR response to exercise and is inversely associated with central obesity.

Oxygen consumption and aerobic metabolism are regulated by three mechanisms: (1) ventilation, (2) cardiac output, and (3) metabolism in the mitochondria.[19,63] Because OSA was not linked to any impairment of ventilation or ventilatory responses to exercise, the decreased VO_2peak must be a consequence of cardiovascular or mitochondrial dysfunction. In adult literature, the low VO_2peak is attributed to the down regulation of cardiac beta-receptors or an altered baroreflex set-point.[54] A second hypothesis is that OSA impairs aerobic metabolism in muscle tissue as an adaptive measure to nocturnal hypoxia.[64,65]

Our findings suggest that cardiovascular function is the major limiting factor for exercise in children with OSA. OSA in children has been linked to increased sympathetic activity at rest and a blunted response to stress,[11] resulting in increased secretion of adrenaline and noradrenaline[12,66] that correlates with AHI and nadir SpO_2.[12,14] Catecholamines were not measured in this study, but elevated catecholamine concentrations at rest may be associated with a blunted sensitivity response to stress, thus impairing the HR and cardiac output's response to exercise.

An interesting finding was that cortical arousals may be more influential than hypoxia because the respiratory arousal index correlated highly with cardiac output at peak exercise capacity. This hypothesis is supported by our results, whereby healthy-weight children with mild OSA had a significantly higher arousal index but their nadir SpO_2 was not significantly different from that of weight-matched children without OSA

(results not shown). The concept that cardiovascular activity is influenced by arousals and cortical activity is also supported by O'Driscoll et al.,[67] who reported that the surge in HR activity immediately after obstructive events during sleep correlates with subcortical arousals and not oxygen desaturation.

Impaired cardiac output response to stress may also be a consequence of hypoxia during sleep as other research has shown that individuals have a blunted HR response when exposed to hypoxic environments. For instance, individuals exposed to high altitude conditions have an elevated resting HR and a decreased peak HR.[68] Lundby et al. compared cardiopulmonary exercise tests at sea level and at high altitude (highest elevation 6,300 m).[69] With increasing altitude, workload and peak HR significantly decreased from 191 ± 3.3 bpm at sea level to 165 ± 1.3 bpm at 6,300 m altitude with no change in adrenaline, noradrenaline, or lactate concentrations from sea level to altitude.

There are several limitations to this study. Although the study was performed at a tertiary pediatric hospital over 2.5 years, it was difficult to identify healthy-weight children with OSA, and obese children without OSA between age 7–12 y. A second limitation was the difficulty recruiting nonsnorers and our 'no OSA' group included snorers without OSA but the small study numbers did not permit comparisons between snorers and nonsnorers without OSA. Only children who successfully completed the exercise test were included in the analysis, so some children were excluded because they could not reach the pedals, became too anxious during the exercise test, or could not ride a bike. Surprisingly, a number of children had never ridden a bike prior to this study and were excluded because of this. No child required a bronchodilator following the exercise test, but no child repeated spirometry after the test to formally exclude exercise-induced asthma.

This is the first study to evaluate cardiac output during exercise in children with OSA and to evaluate whether exercise dysfunction in obese children is influenced by the presence of OSA. Obesity and OSA were found to be independently linked to exercise restriction in children. Obesity reduces a child's exercise tolerance because they have to carry a heavier body mass and are physically deconditioned. Our hypothesis that OSA reduces a child's exercise capacity through a blunted cardiac response to stress is supported by our findings that these children have reduced peak HR, stroke volume index, and cardiac output at peak exercise capacity compared to those without OSA. Both conditions also independently reduce VO_2 peak. Thus, children who are obese and have OSA are more exercise limited and have a lower cardiac output and VO_2 peak than children who have OSA or obesity. Longitudinal research is needed to evaluate if these findings translate into risk for early cardiovascular disease.

ACKNOWLEDGMENTS

We would like to thank Professor Jennifer Peat, Mr Ihsan Savran, and the staff from the David Read Sleep Unit, Respiratory Function Unit, The Children's Hospital Institute of Sport's Medicine and Weight Management Service at The Children's Hospital at Westmead for contributing and supporting this study. We would also like to thank the children and families who participated in this study.

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Evans was supported by a National Health and Medical Research Council Biomedical Postgraduate Scholarship (#571242). Dr. Evans is currently employed with ResMed Ltd., Bella Vista NSW Australia. This employment commenced after the completion of this project (including participant recruitment, data collection and analysis). ResMed Ltd. has no affiliation with this specific project or manuscript. The other authors have indicated no financial conflicts of interest. The work was performed at the Children's Hospital at Westmead, Westmead, NSW Australia

REFERENCES

1. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. Am J Respir Crit Care Med 1999;159:1527-32.
2. Shi Z, Taylor AW, Gill TK, Tuckerman J, Adams R, Martin J. Short sleep duration and obesity among Australian children. BMC Public Health 2010;10:609.
3. Silva GE, Goodwin JL, Parthasarathy S, et al. Longitudinal association between short sleep, body weight, and emotional and learning problems in Hispanic and Caucasian children. Sleep 2011;34:1197-205.
4. Amin RS, Kimball TR, Bean JA, et al. Left ventricular hypertrophy and abnormal ventricular geometry in children and adolescents with obstructive sleep apnea. Am J Respir Crit Care Med 2002;165:1395-9.
5. Amin RS, Kimball TR, Kalra M, et al. Left ventricular function in children with sleep-disordered breathing. Am J Cardiol 2005;95:801-4.
6. Tal A, Leiberman A, Margulis G, Sofer S. Ventricular dysfunction in children with obstructive sleep apnea: radionuclide assessment. Pediatr Pulmonol 1988;4:139-43.
7. Shiomi T, Guilleminault C, Stoohs R, Schnittger I. Obstructed breathing in children during sleep monitored by echocardiography. Acta Paediatr 1993;82:863-71.
8. 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.
9. Snow AB, Khalyfa A, Serpero LD, et al. Catecholamine alterations in pediatric obstructive sleep apnea: effect of obesity. Pediatr Pulmonol 2009;44:559-67.
10. McConnell K, Somers VK, Kimball T, et al. Baroreflex gain in children with obstructive sleep apnea. Am J Respir Crit Care Med 2009;180:42-8.
11. Chaicharn J, Lin Z, Chen ML, Ward SL, Keens T, Khoo MC. Model-based assessment of cardiovascular autonomic control in children with obstructive sleep apnea. Sleep 2009;32:927-38.
12. O'Driscoll DM, Horne RS, Davey MJ, et al. Increased sympathetic activity in children with obstructive sleep apnea: cardiovascular implications. Sleep Med 2011;12:483-8.
13. McConnell K, Somers VK, Kimball T, et al. Baroreflex gain in children with obstructive sleep apnea. Am J Respir Crit Care Med 2009;180:42-8.
14. 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.
15. Dubern B, Tounian P, Medjadhi N, Maingot L, Girardet JP, Boule M. Pulmonary function and sleep-related breathing disorders in severely obese children. Clin Nutr 2006;25:803-9.
16. Marcus CL, Curtis S, Koerner CB, Joffe A, Serwint JR, Loughlin GM. Evaluation of pulmonary function and polysomnography in obese children and adolescents. Pediatr Pulmonol 1996;21:176-83.
17. 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.
18. Marcus CL, Gozal D, Arens R, et al. Ventilatory responses during wakefulness in children with obstructive sleep apnea. Am J Respir Crit Care Med 1994;149:715-21.
19. Weisman IM, Beck KC, Casaburi R, et al. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211-77.

20. Sarullo FM, Fazio G, Brusca I, et al. Cardiopulmonary exercise testing in patients with chronic heart failure: prognostic comparison from peak VO2 and VE/VCO2 slope. Open Cardiovasc Med J 2010;4:127-34.
21. Ingle L, Sloan R, Carroll S, Goode K, Cleland JG, Clark AL. Prognostic significance of different measures of the ventilation-carbon dioxide relation in patients with suspected heart failure. Eur J Heart Fail 2011;13:537-42.
22. Myers J, Gullestad L, Vagelos R, et al. Cardiopulmonary exercise testing and prognosis in severe heart failure: 14 mL/kg/min revisited. Am Heart J 2000;139:78-84.
23. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med 1992;327:1785-8.
24. Damianidou L, Eboriadou M, Giannopoulos A, et al. Reduced exercise capacity in Greek children with mild to moderate obstructive sleep apnea syndrome. Pediatr Pulmonol 2013;48:1237-45.
25. Mallory GB, Jr., Fiser DH, Jackson R. Sleep-associated breathing disorders in morbidly obese children and adolescents. J Pediatr 1989;115:892-7.
26. Verhulst SL, Schrauwen N, Haentjens D, et al. Sleep-disordered breathing in overweight and obese children and adolescents: prevalence, characteristics and the role of fat distribution. Arch Dis Child 2007;92:205-8.
27. Wing YK, Hui SH, Pak WM, et al. A controlled study of sleep related disordered breathing in obese children. Arch Dis Child 2003;88:1043-7.
28. Xu Z, Jiaqing A, Yuchuan L, Shen K. A case-control study of obstructive sleep apnea-hypopnea syndrome in obese and nonobese Chinese children. Chest 2008;133:684-9.
29. Li AM, Chan MH, Chan DF, et al. Insulin and obstructive sleep apnea in obese Chinese children. Pediatr Pulmonol 2006;41:1175-81.
30. Goran M, Fields DA, Hunter GR, Herd SL, Weinsier RL. Total body fat does not influence maximal aerobic capacity. Int J Obes Relat Metab Disord 2000;24:841-8.
31. Zanconato S, Baraldi E, Santuz P, et al. Gas exchange during exercise in obese children. Eur J Pediatr 1989;148:614-7.
32. Rowland T, Bhargava R, Parslow D, Heptulla RA. Cardiac response to progressive cycle exercise in moderately obese adolescent females. J Adolesc Health 2003;32:422-7.
33. Rowland TW. Effect of obesity on cardiac function in children and adolescents: a review. J Sports Sci Med 2007;6:319-26.
34. Unnithan VB, Baynard T, Potter CR, et al. An exploratory study of cardiac function and oxygen uptake during cycle ergometry in overweight children. Obesity (Silver Spring) 2007;15:2673-82.
35. Schuster I, Karpoff L, Perez-Martin A, et al. Cardiac function during exercise in obese prepubertal boys: effect of degree of obesity. Obesity 2009;17:1878-83.
36. Franco RA, Jr., Rosenfeld RM, Rao M. First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. Otolaryngol Head Neck Surg 2000;123:9-16.
37. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Adv Data 2000:1-27.
38. Garnett SP, Baur LA, Cowell CT. Waist-to-height ratio: a simple option for determining excess central adiposity in young people. Int J Obes 2008;32:1028-30.
39. Loughlin GM, Brouillette RT, Brooke LJ, et al. Standards and indications for cardiopulmonary sleep studies in children. Am J Respir Crit Care Med 1996;153:866-78.
40. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. 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.
41. Katz ES, Marcus CL. Diagnosis of obstructive sleep apnea syndrome in infants and children. In: Sheldon SH, Ferber R, Kryger MH, eds. Principles and Practice of Pediatric Sleep Medicine. Philadelphia, PA: Elsevier Saunders, 2005:197-210.
42. Melendres MC, Lutz JM, Rubin ED, Marcus CL. Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing. Pediatrics 2004;114:768-75.
43. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540-5.
44. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
45. Wang X, Dockery DW, Wypij D, Fay ME, Ferris Jr BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15:75-88.
46. USCOM. USCOM the measure of life: the basics. In. 1.8.0.0 ed. Sydney, NSW, Australia: USCOM, 2008:1-52.
47. Boyd E. The Growth of the Surface Area of the Human Body. Minneapolis, MN: University of Minnesota Press, 1935.
48. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377.
49. Lamb KL. Exercise regulation during cycle ergometry using the children's effort rating table (CERT) and rating of perceived exertion (RPE) scales. Pediatric Exercise Science 1996;8:337-50.
50. Hommerding PX, Donadio MV, Paim TF, Marostica PJ. The Borg scale is accurate in children and adolescents older than 9 years with cystic fibrosis. Respir Care 2010;55:729-33.
51. Cooper D, Weiler-Ravell D. Gas exchange response to exercise in children. Am Rev Respir Dis 1984;129:S47-8.
52. Tabachnick BG, Fidell LS. Using Multivariate Statistics. 4th ed. Boston, MA: Allyn and Bacon, 2001.
53. Alonso-Fernandez A, Garcia-Rio F, Arias MA, et al. Obstructive sleep apnoea-hypoapnoea syndrome reversibly depresses cardiac response to exercise. Eur Heart J 2006;27:207-15.
54. Kaleth AS, Chittenden TW, Hawkins BJ, et al. Unique cardiopulmonary exercise test responses in overweight middle-aged adults with obstructive sleep apnea. Sleep Med 2007;8:160-8.
55. Vanhecke TE, Franklin BA, Zalesin KC, et al. Cardiorespiratory fitness and obstructive sleep apnea syndrome in morbidly obese patients. Chest 2008;134:539-45.
56. Przybylowski T, Bielicki P, Kumor M, et al. Exercise capacity in patients with obstructive sleep apnea syndrome. J Physiol Pharmacol 2007;58 Suppl 5:563-74.
57. Fredriksen P, Ingjer F, Nystad W, Thaulow E. A comparison of VO2peak between patients with congenital heart disease and healthy subjects, all aged 8-17 years. Eur J Appl Physiol 1999;80:409-16.
58. Ucok K, Aycicek A, Sezer M, et al. Aerobic and anaerobic exercise capacities in obstructive sleep apnea and associations with subcutaneous fat distributions. Lung 2009;187:29-36.
59. Lin CC, Hsieh WY, Chou CS, Liaw SF. Cardiopulmonary exercise testing in obstructive sleep apnea syndrome. Respir Physiol Neurobiol 2006;150:27-34.
60. Rowland T, Goff D, Martel L, Ferrone L. Influence of cardiac functional capacity on gender differences in maximal oxygen uptake in children. Chest 2000;117:629-35.
61. Giordano U, Ciampalini P, Turchetta A, et al. Cardiovascular hemodynamics: relationships with insulin resistance in obese children. Pediatr Cardiol 2003;24:548-52.
62. de Simone G, Devereux RB, Daniels SR, et al. Stroke volume and cardiac output in normotensive children and adults. Assessment of relations with body size and impact of overweight. Circulation 1997;95:1837-43.
63. Gallagher CG, Marciniuk DD. Postgraduate course 16: Interpretation of clinical exercise testing for the clinician. In: Dempsey JA, ed. 1st ed. San Francisco, CA: American Thoracic Society, 1997:1-18.
64. Bonanni E, Pasquali L, Manca ML, et al. Lactate production and catecholamine profile during aerobic exercise in normotensive OSAS patients. Sleep Med 2004;5:137-45.
65. Vanuxem D, Badier M, Guillot C, Delpierre S, Jahjah F, Vanuxem P. Impairment of muscle energy metabolism in patients with sleep apnoea syndrome. Respir Med 1997;91:551-7.
66. Snow AB, Khalyfa A, Serpero LD, et al. Catecholamine alterations in pediatric obstructive sleep apnea: effect of obesity. Pediatr Pulmonol 2009;44:559-67.
67. O'Driscoll DM, Foster AM, Ng ML, et al. Acute cardiovascular changes with obstructive events in children with sleep disordered breathing. Sleep 2009;32:1265-71.
68. Gamboa A, Leon-Velarde F, Rivera-Ch M, Vargas M, Palacios JA, Monge CC. Ventilatory and cardiovascular responses to hypoxia and exercise in Andean natives living at sea level. High Alt Med Biol 2001;2:341-7.
69. Lundby C, Araoz M, van Hall G. Peak heart rate decreases with increasing severity of acute hypoxia. High Alt Med Biol 2001;2:369-76.
70. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. Am Rev Respir Dis 1984;129:S49-55.