Cardiovascular Changes in Children with Snoring and Obstructive Sleep Apnoea

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Abstract

Introduction: Adults with obstructive sleep apnoea (OSA) are well documented to be at high risk for cardiovascular abnormalities. Growing evidence suggests that OSA is also associated with cardiovascular consequences in children. The purpose of this review is to examine the available data on this association in children. Methods: Primary studies were extracted from a MEDLINE search limited to those published between 1970 and 2008. The keywords used included child, sleep disordered breathing, sleep apnoea, snoring, blood pressure and hearts. The relevant articles were selected by consensus between 2 authors. Results: The results suggested that OSA was consistently associated with hypertension. Meta-analysis of risk of hypertension in those with high apnoea-hypopnoea index was undertaken. A combined odds ratio equal to 3.15 was found (95% confidence interval, 2.01 to 4.93). There was evidence for increased sympathetic activation, decreased arterial distensibility and ventricular hypertrophy in children with OSA. Conclusion: Childhood OSA is associated with blood pressure dysregulation. The association of OSA with other cardiovascular morbidities requires further study in view of the limited data available currently.

Key words: Atherosclerosis, Child, Hypertension

Introduction

Sleep disordered breathing (SDB) is a spectrum of diseases ranging from primary snoring to obstructive sleep apnoea (OSA). A recent review suggested that the prevalence of childhood OSA diagnosed by varying criteria was 1% to 4%. In the same review, the prevalence of snoring (a common symptom of SDB) was estimated to be 7.45% [95% confidence interval (CI), 5.75 to 9.61] in children.

In patients with OSA, there are intermittent episodes of complete or partial obstruction leading to intermittent desaturations and/or arousals. This would result in either stimulation of sympathetic system or suppression of the vagal tone that may persist beyond sleep. The disturbance of the autonomic nervous system would result in significant changes in the cardiovascular system. The process of intermittent hypoxaemia and subsequent re-oxygenation also damages the endothelium because of the generation of free radicals. Furthermore, the excessive negative intrathoracic pressure swing generated during the obstruction would also affect cardiac functions. In adults, OSA has been well documented to be associated with cardiovascular abnormalities such as hypertension, ischaemic heart disease, arrhythmia and heart failure. The purpose of the current review is to examine the current data about this association in children.

Methods

Primary studies were extracted from a MEDLINE search limited to those published from 1970 to 2008. The keywords used included child, SDB, sleep apnoea, snoring, blood pressure (BP), heart, hypertrophy, heart rate variability and endothelium. The relevant articles were selected by consensus between 2 authors (KLK and DKN). The methods of meta-analysis on the relationship of hypertension and high apnoea-hypopnoea index (AHI) were reported previously. In the current analysis, the fixed effect meta-analysis (i.e. Mantel-Haenszel methods) was used because no evidence of heterogeneity existed in our pooled studies of hypertension and C-reactive protein (CRP) at 5% level (Test for heterogeneity, $P = 0.538$ and 0.213 respectively).

Blood Pressure

It was first reported that BP would be elevated in patients with sleep apnoea in 1976 by Guilleminault et al. They found that 5 out of 8 children with OSA were hypertensive...
while awake, rather than during sleep when apnoea occurred. Subsequently, there were other case reports of children with upper airway obstruction and severe hypertension.\(^7,8\) These were all very young paediatric patients aged less than 6 years old and they had hypertension as defined by adult values, i.e. >140/80. Most paediatric patients with sleep apnoea would not have BP as high as 140/80 mmHg. In a later paediatric study by Marcus et al,\(^9\) hypertension was defined as BP exceeding the 95th percentile for the age and height percentile.\(^10\) Marcus et al quantified BP alteration using ‘Blood Pressure Index’ (BP index = measured BP–BP at 95th centile with reference to height and age). They found that children with OSA had a higher risk for hypertension than the group with primary snoring and that diastolic blood pressure (DBP) was higher in the group with OSA. There was positive correlation between both systolic blood pressure (SBP) and DBP and severity of sleep apnoea. However, this study was not ideal as Marcus et al used subjects who snored as controls. The current authors reported that BP was significantly higher in the group of AHI >5/hour. However, they could not demonstrate such a relationship in daytime BP.

Guilleminault et al\(^13\) reported a prospective study of 78 children who underwent polysomnography (PSG), tilt table and BP measurement. They identified 8 children who had abnormal BP [7 with low BP (defined as SBP <85 and DBP <60 mmHg) and 1 with high BP]. Furthermore, they found that those with OSA had a significantly larger drop in BP during tilt table test and this drop would normalise after implementation of continuous positive pressure ventilation. The authors concluded that children with OSA without concomitant hypoxaemia would have low BP as a result of increased parasympathetic tone.

Ambulatory blood pressure (ABP) monitoring is currently regarded as a more accurate measure of BP because ABP correlates better with end-organ damages.\(^14\) Amin et al\(^15\) quantified BP using another BP index [(Measured BP–95th percentile of BP)/95th percentile BP x 100]. Three abnormal findings of BP were noted, namely nocturnal hypertension, decreased nocturnal dipping and increased BP variability. They found that diastolic BP during wakefulness was significantly lower in patients with sleep apnoea and there was a significant negative correlation with the severity of OSA. They proposed that this might be due to the abnormal elastic recoil of vessels. Also, they noted that there was a dose-dependent increase in BP variability with the severity of OSA, during sleep and while awake. It is important to note that daytime systolic ambulatory BP variability was related to cardiovascular mortality\(^16\) and the presence of periventricular white matter lesion in adults.\(^17\)

A further study by Amin et al\(^18\) reported higher BP load in the group with AHI >5 than the group with lower AHI and control subjects. They found an exaggerated BP surge in the morning even in children with AHI between 1.0 and 5.0. The morning BP surge was defined as the slope of BP from the beginning of the last hour of sleep to the end of the first hour of awakening. The systolic slopes, described by the adjusted least square estimates ± SEM, were 0.4 ± 0.9, 2.8 ± 0.9 and 3.5 ± 0.9 for healthy controls, mild SDB and severe SDB, respectively. The slopes for DBP for these groups were 0.8 ± 0.8, 2 ± 0.9 and 2.7 ± 0.9, respectively. This surge was more marked in the group with AHI >5. This exaggerated morning BP surge has been shown to be a predictor for the development of increased carotid intima thickness,\(^19\) myocardial hypertrophy/infarction\(^20\) and stroke.\(^21\)

Obesity is a potent confounding factor in the study of OSA and BP in children. Reade et al\(^22\) reported a study of obese subjects (n = 56). Obese subjects with hypertension had a significantly higher incidence of OSA as defined by AHI >1.5/hour\(^23\) than their normotensive counterpart (64% vs 29%).

Leung et al\(^24\) reported that obese children in the high AHI group, i.e. >5, had a higher incidence of hypertension as recorded by ABP monitoring than subjects in the low AHI group [odds ratio (OR), 6.67; 95% CI, 1.00 to 44.28]. Another similar study by Li et al\(^25\) suggested that children with AHI >5 had a significantly higher prevalence of nocturnal systolic hypertension (OR, 3.9; 95% CI, 1.4 to 10.5) and diastolic hypertension (OR, 3.5; 95% CI, 1.4 to 8.1) than AHI <5 and compared to those without snoring by ABP monitoring.

The authors previously reported a meta-analysis of AHI and hypertension that showed a significantly higher risk of hypertension in those with high AHI (OR, 3.37; 95% CI, 1.56 to 7.25).\(^4\) We updated this meta-analysis by incorporating new studies by Reade et al\(^22\) and Li et al.\(^25\) The combined OR was 3.15 with a much shorter 95% CI (2.01 to 4.93, Fig. 1). In another meta-analysis, Zintzaras and Kadjitis\(^26\) included both sleep polysomnographic studies and epidemiological studies. With this heterogeneous group that included both primary snoring and OSA, they failed to find a significant association between hypertension and SDB. Nevertheless, they reported that the group with moderate to severe SDB was associated with a 87% and 121% higher risk for elevated SBP and DBP, respectively when compared with the group with mild SDB or no SDB.
Ventricular Hypertrophy

As hypertension is now known to be a complication of sleep apnoea, it is logical to expect the presence of left ventricular hypertrophy (LVH) in these patients. It seems reasonable to hypothesise further that LVH is related to the presence of higher BP.

Both right and left ventricular hypertrophy and enlargement were shown in children with adenotonsillar hypertrophy which improved after adenotonsillectomy.27 Amin et al28 also showed that LV mass index and relative wall thickness were greater in the OSA group compared with those with primary snoring. An AHI >10/hour was significantly associated with RV dimensions and LV mass index above 95th percentile (OR, 6.7 and 11.2 respectively). The same paper reported that neither resting SBP nor DBP were significant predictors for LV mass index or RV dimension adjusted for height in patients with OSA although there was a tendency toward higher BPs in the OSA group compared with the snoring group. Subsequently, the same group18 recruited more subjects and reported that BP parameters were indeed associated with left ventricular remodelling with increased relative wall thickness and LV mass index. In another study on adolescents, significant differences in the echocardiographic parameters including LV posterior wall thickness, deceleration time of early diastolic flow and isovolumetric relaxation time were found between the OSA group defined as either respiratory disturbance index (RDI) ≥5 or RDI ≥10 during supine position or desaturation index ≥5, and the control group.29 Meta-analysis could not be performed because of incompatible outcome measures among studies.

Ventricular Functions

Before clinical signs of cardiac involvement could be detected, ventricular dysfunction had been demonstrated in young children (mean age of 3.5 years) who had features of OSA (as defined by OSA score of ≥3.5)30 with the use of radionuclide ventriculography.31 Reduced right ventricular ejection fraction and wall motion abnormalities were detected in the OSA group which improved after adenotonsillectomy. Left ventricular ejection fraction also rose after the operation.

Diastolic function of the LV relates to chamber stiffness and relaxation following ventricular contraction. An assessment of mitral inflow pattern is one of the methods in assessing the diastolic function of LV. E-wave is the result of passive early diastolic LV filling and A-wave represents active late diastolic LV filling due to LA contraction. A decrease in E/A is used as a marker for diastolic function. There was a dose-dependent relationship between a decrease in E/A and an increase in the severity of OSA and this altered diastolic function normalised after treatment with either continuous positive airway pressure (CPAP) or adenotonsillectomy.32 However, assessment of diastolic function of LV is complex and using 1 parameter alone may not present the true picture.

Despite the fact that many studies demonstrate impaired ventricular function in SDB,32,33 heart failure was uncommon in children with OSA. James et al34 studied 271 SDB children treated with adenotonsillectomy and only 1 child with congenital heart disease had signs of heart failure preoperatively.

Cor pulmonale

Children with upper airway obstruction were more likely to have cor pulmonale if they had concomitant underlying chronic lung diseases.3,5,15 Sometimes, cor pulmonale might be the main presenting feature of OSA. Hunt and Brouilette36 reported that 16 OSA infants had significant, otherwise unexplained, cor pulmonale at the time of referral to a sleep
study. The same group also reported that 12 of 22 young patients with OSA (55%) had cor pulmonale. The total number of children younger than 12 years with OSA-caused cor pulmonale reported in the literature was 31 with the youngest being less than 1 year old. Increased awareness of OSA and early cardiovascular examination of the patients with OSA might help to result in earlier treatment and less morbidity.

**Heart Rate Variability**

While sympathetic activation has been proposed to be the underlying mechanism for hypertension, left ventricular hypertrophy and abnormal diastolic function, many researchers tried to study the autonomic nervous control in patients with OSA by using heart rate variability as the surrogate marker. In the early study, qualitative assessment of heart rate variability using Poincare Plot was employed. To have a quantitative assessment of heart rate variability, parameters were analysed under the time domain and frequency domain. The technique of power spectral analysis was employed to study the frequency parameters. For the frequency domain, high frequency is a marker of vagal activity while low frequency represents both sympathetic activity and vagal activity. It was shown that OSA patients had higher LF activity or LF/HF ratio. Baharav et al found that the 10 children with RDI >2 had higher LF/HF ratio while awake and during sleep when compared with those with RDI ≤2.

**Arterial Tone**

*Pulse Wave Velocity*

As sympathetic activity was believed to be an increase in OSA, it was not surprising that the tone of the vessel would be altered. Measuring pulse wave velocity (PWV) is one way to assess the resting arterial tone. PWV, which measures how fast a pulse travels from one point to the other, is inversely proportional to the arterial wall stiffness which, in turn, is determined by BP. It is a non-invasive marker for arousal. Arousal that occurred at the termination of an obstructive event will cause transient increase in BP and thus a shorter PTT. PTT arousal, defined as a decline in the average PTT signals of ≥15 ms for at least 5 seconds was related to an OSA episode in adults. PTT arousal index is the average number of PTT arousal episodes per hour of sleep time. Katz et al demonstrated that children with UARS (Upper Airway Resistance Syndrome) had a significantly higher PTT arousal index than primary snorers (6.8 events per hours versus 2.2 events per hour). Brietzke et al proposed a cut-off point for PTT arousal index of 5.4 events per hour to be suggestive of OSA in children. This cut-off point had a sensitivity of 81% and specificity of 76% to detect OSA, defined as AHI >1.

**Endothelial Function**

There has been increasing evidence that showed the association of endothelial dysfunction and adverse cardiovascular events. Endothelial function is affected in adults with OSA. The proposed mechanisms of OSA affecting the endothelial function were diverse. Firstly, production of vasoactive substances by endothelial cells could be altered in response to nocturnal hypoxaemia as a result of SDB, i.e. an increase in endothelin production and decrease in nitric oxide production. As a result, there would be hypertension resulting from vasoconstriction. Secondly, inflammation may be an important factor contributing to endothelial dysfunction by increasing adherence of inflammatory mediators to endothelial cells and hypercoagulability. Thirdly, sympathetic activation may exert a direct effect on the endothelium to cause vasoconstriction. Furthermore, a genetic predisposition might also play a role. Endothelial function could be assessed by the degree of post-occlusive hyperemia. This response was shown to be consistently blunted in children with OSA and such altered endothelial function was reversible 4 to 6 months after adenotonsillectomy. Gozal et al conducted a cuff-occlusion test in 26 OSA children, defined as obstructive apnoea index larger than 1 and/or AHI >5 with a nadir oxygen saturation value <92%, and 8 matched controls. All subjects in this study were non-obese. OSA children were retested 4 to 6 months after adenotonsillectomy. They showed that OSA children had significantly slower hyperemic responses than controls preoperatively (69.1 s in controls vs 113 s in OSA children, P < 0.001). Postoperatively, hyperemic responses in OSA children were similar to the controls indicating that altered endothelial function was reversed with the treatment of OSA.
**Inflammation/Atherosclerosis**

Growing evidence suggests that OSA is associated with atherosclerosis in adults. Recent research of OSA found that inflammation was involved in the process.

C-reactive protein (CRP) is a sensitive marker for systemic inflammation and an important factor for atherosclerosis that predicts increased risk of coronary heart disease. CRP was shown to increase in children with SDB. However, another study using younger and leaner subjects could not confirm the same relationship. Meta-analysis of the mean difference between log CRP level in those with AHI >5 and AHI <1 extracted from Tauman et al and Kaditis et al gave a combined mean difference of 0.33 with a 95% CI equal to 0.143 to 0.516 (Z test, \( P < 0.001 \), Fig. 2). The study by Li et al was excluded from the meta-analysis because their report did not provide the mean and standard deviation of CRP level. CRP was found to drop after tonsillo-adenoidecotomy in children.

OSA with apnoea-induced hypoxaemia and exaggerated negative intrathoracic pressure, arousals from sleep, surges in BP, alteration in autonomic nervous activity, as well as production of reactive oxygen species, vascular endothelial growth factor and inflammatory mediators are factors contributing to the cardiovascular consequences. It has been hypothesised that various cardiovascular complications could be mediated through accelerated atherosclerosis. Other factors that might be involved in atherosclerosis, such as fibrinogen level and p-selectin (marker of platelet activation), were also shown to be higher in those with SDB.

**Cerebral Artery**

Adults with OSA have an increased risk of cerebro-vascular disease independent of atherosclerotic risk factors. Limited research has been done in this aspect in children with OSA. Hill et al found that snoring children with an AHI >5 had significantly raised middle cerebral artery blood flow velocities compared with non-snoring children. Hill et al also showed significant differences in indices of cognition (processing speed and visual attention) and behaviour (Behavior Rating Inventory of Executive Function) between snoring children with an AHI >5 and non-snoring controls. However, the relationships became non-significant after being adjusted for the increase in middle cerebral artery blood flow. The results of Hill et al’s study suggested that an increase in middle cerebral artery blood flow velocity contributed by OSA might be related to the deterioration in cognition and behaviour in children with OSA.

**Conclusion**

OSA results in episodic desaturation, increased arousal during sleep and increased negative intra-thoracic pressure during obstruction. All these phenomena affect different parts of the cardiovascular system resulting in morbidities and eventual mortalities. It would be important for all medical practitioners dealing with childhood OSA to be familiar with the assessment of these cardiovascular effects of childhood OSA because the presence of these effects could help quantify the severity of OSA and thus guide management.

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