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Review

Physiological effects of obstructive sleep apnea syndrome in childhood☆

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ABSTRACT

Sleep disordered breathing in children refers to a group of respiratory disorders that occur or are exacerbated during sleep. Obstructive sleep apnea syndrome (OSAS) is one of the most significant disorders in this group. OSAS can present in all age groups from early infancy to adolescent years. The cardinal feature of OSAS is limitation of inspiratory flow and volume during sleep resulting in abnormal gas exchange and/or alteration of sleep patterns. When OSAS is a chronic condition it often results in adverse physiological effects that impact on health and development. The present review discusses genesis of OSAS in children and consequent end organ injury with special emphasis on behavior and cognition, cardiovascular function, autonomic regulation, inflammation, endothelial function and metabolic syndrome.

1. Introduction

Sleep disordered breathing (SDB) in children refers to a group of respiratory disorders that occur or are exacerbated during sleep such as apnea of prematurity, central apnea, hypoventilation, and obstructive sleep apnea syndrome (OSAS). These manifest with limitation of inspiratory flow and volume, and/or alterations in respiratory rhythm, resulting in abnormal gas exchange and/or altered sleep patterns. When these become chronic they often lead to significant adverse physiological effects that impact on health and development. The present review discusses the genesis of OSAS and presents the principle concepts and mechanisms that link OSAS in children to end organ injury.

2. The spectrum of sleep disordered breathing

In general, disorders categorized as SDB are stratified according to the nature of the main respiratory anomaly. These include disorders associated primarily with central sleep apnea, disorders associated primarily with non-obstructive hypoventilation, and disorders associated with the spectrum of obstructive sleep disordered breathing.

The international classification of sleep disorders (ICSD-2) refers to the medical etiology associated with each disorder within the above stratifications (Table 1) (2005). Although most types of SDB according to the ICSD-2 are not classified by age, all exist in children. It should be emphasized that children may present with more than one type of respiratory perturbation during sleep. For example, a child with Duchenne muscular dystrophy may exhibit both non-obstructive hypoventilation and OSAS. Accordingly, diagnoses will include "Sleep related hypoventilation/hypoxemia due to neuromuscular or chest wall diseases" and "Obstructive sleep apnea, Pediatrics").

Within each of the main SDB categories, the ICSD-2 does refer to three disorders associated with children. (1) *Primary sleep apnea of infancy* – a disorder that mostly affects premature infants but may extend to early infancy. It is characterized by either central or obstructive apneas or hypopneas, or mixed events, and manifests with significant physiological compromise including hypoxemia and bradycardia. The disorder is considered to be related with brainstem immaturity. However, a variety of medical conditions such as anemia, gastro-esophageal reflux disease (GERD), and various metabolic disorders, may perpetuate the condition. Medical treatment such as caffeine and continuous respiratory and heart rate monitoring during sleep are standard of care. However, improvement is expected after the early weeks of life. (2) *Congenital central hypoventilation syndrome (CCHS)* – a medical disorder that historically has been described in childhood but is now recognized in greater numbers in adults. This is an autosomal dominant disease of abnormal neurological development caused by abnormalities in function of the PHOX2B gene (Weese-Mayer et al., 2010). This disorder bears the hallmark of life-threatening hypoventilation during sleep, autonomic dysfunction and deficient responses

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Table 1
Sleep disordered breathing.

A.	Disorders associated primarily with central apnea
	1. Primary central sleep apnea
	Idiopathic
	2. Cheyne Stokes breathing pattern
	Congestive heart failure, stroke, renal failure
	3. High altitude periodic breathing
	Recent ascent to altitude of >4000 meters
	4. Central sleep apnea due to medical condition, not Cheyne Stokes
	Brainstem lesions of vascular, structural, neoplastic, degenerative, or traumatic nature
	5. Central sleep apnea due to drug or substance
	Methadone or other narcotics
	6. Primary sleep apnea of infancy (Formerly primary sleep apnea of newborn)[a]
B.	Disorders associated primarily with non-obstructive hypoventilation
	7. Sleep related non-obstructive alveolar hypoventilation, idiopathic
	8. Sleep related hypoventilation/hypoxemia due to pulmonary parenchymal or vascular pathology
	Autoimmune disorders affecting lung, pulmonary hypertension, sickle cell anemia
	9. Sleep related hypoventilation/hypoxemia due to lower airways diseases
	Asthma, cystic fibrosis, bronchiectasis
	10. Sleep related hypoventilation/hypoxemia due to neuromuscular and chest wall disorders
	Duchenne muscular dystrophy, spinal muscular atrophy, kyphoscoliosis
	11. Congenital central alveolar hypoventilation syndrome (CCHS)[a]
C.	Disorders associated primarily with obstructive sleep disordered breathing
	12. Obstructive sleep apnea, Adult
	13. Obstructive sleep apnea, Pediatrics[a]

Modified from the international classification of sleep disorders, diagnostic and coding manuel, 2nd edition.
[a] Disorders that specifically present in children.

to hypoxemia and hypercarbia. CCHS usually requires lifelong medical support and expertise to maintain life and minimize morbidity. Recently, another disease with central hypoventilation and autonomic dysfunction – rapid-onset obesity with hypothalamic dysfunction, hypoventilation and autonomic dysregulation (ROHHAD) has been described in children (Ize-Ludlow et al., 2007). However, covering the entire spectrum of sleep disordered breathing in children is beyond the scope of this review which will focus on the most common form of sleep disordered breathing in children – obstructive SDB that predominantly results from obstruction to airflow at the pharynx. (3) *Obstructive sleep apnea, Pediatric* – is the most significant and studied form of SDB in children, and will be the major focus of discussion as one of the disorders within the spectrum of obstructive sleep disordered breathing.

Obstructive sleep disordered breathing

Obstructive sleep disordered breathing in children include three distinct phenotypes: *Primary snoring (PS)*, *Upper airway resistance syndrome (UARS)*, and *OSAS*. These disorders may be considered as a continuum in terms of their medical impact of physiological effects.

Primary snoring is defined as snoring that is not associated with apnea or hypopnea, gas exchange abnormalities (hypoxemia/hypercarbia), or sleep interruption (2002). The incidence in children is varies between reports and ranges from 1.5% to 27.6% (Marcus et al., 2012). In the past, PS has not been considered to be associated with systemic physiological effects. However, recent studies suggest the contrary and neurocognitive deficits have been reported in school age children (Brockmann et al., 2012; Giordani et al., 2008).

Upper airway resistance syndrome is a respiratory disorder associated with snoring, flow limitation, and sleep disruption without gas exchange abnormalities. This disorder was first described as progressive increase in inspiratory negative intrathoracic pressures (measured by esophageal manometry) terminated by an arousal leading to sleep fragmentation, in the absence of apneas, hypopneas, or oxygen desaturations (Guilleminault et al., 1982). These arousal events are often referred to as respiratory effort related arousals (RERAs) (Iber et al., 2007a). The introduction of nasal pressure waveform recording with routine polysomnography has facilitated detection of flow limitation in UARS without esophageal manometry. In children, UARS has been associated with neurobehavioral changes similar to those of OSAS and responds to similar treatments despite not being associated with discrete respiratory events or gas exchange abnormalities (Lumeng and Chervin, 2008). Currently, UARS does not have a separate International Classification of Diseases code and is clinically grouped within the spectrum of obstructive sleep disordered breathing disorders.

Obstructive sleep apnea syndrome (OSAS) is the extreme end of the spectrum of obstructive sleep disordered breathing in children. It is characterized by recurrent events of partial or complete upper airway obstruction during sleep resulting in disruption of normal ventilation, arousals, and disrupted sleep architecture (2005). OSAS may present in a continuum of mild, moderate, or severe forms according to the number of respiratory events, severity of gas exchange abnormalities, and the amount of sleep disruption. These can produce long term effects on children including alterations in behavior, neurocognitive deficits, cardiovascular morbidities, autonomic dysregulation, and inflammatory and metabolic derangements that are discussed in Section 5.

The estimated prevalence of OSAS in childhood ranges from 1.2% to 5.7%, it peaks between 2 and 8 years of age, and is usually associated with adenotonsillar hypertrophy (Marcus et al., 2012). However, OSAS can occur in children of all ages, even those having normal sized tonsils and adenoids, or those having undergone adenotonsillectomy. As early as the neonatal period, underlying conditions such as craniofacial anomalies affecting upper airway structure, and neurological disorders affecting upper airway neuromotor tone may lead to airway obstruction during sleep. Later onset of symptoms, particularly when associated with obesity, may be seen during school-age and adolescent years and in some populations the incidence may exceed 50% (Arens and Muzumdar, 2010). The diagnosis of childhood OSAS continues to progress as morbidities are better characterized and more diagnostic tools become available.

Understanding the pathophysiological mechanisms leading to each of the above phenotypes is important in order to direct the most effective care. For all three phenotypes, physiologic

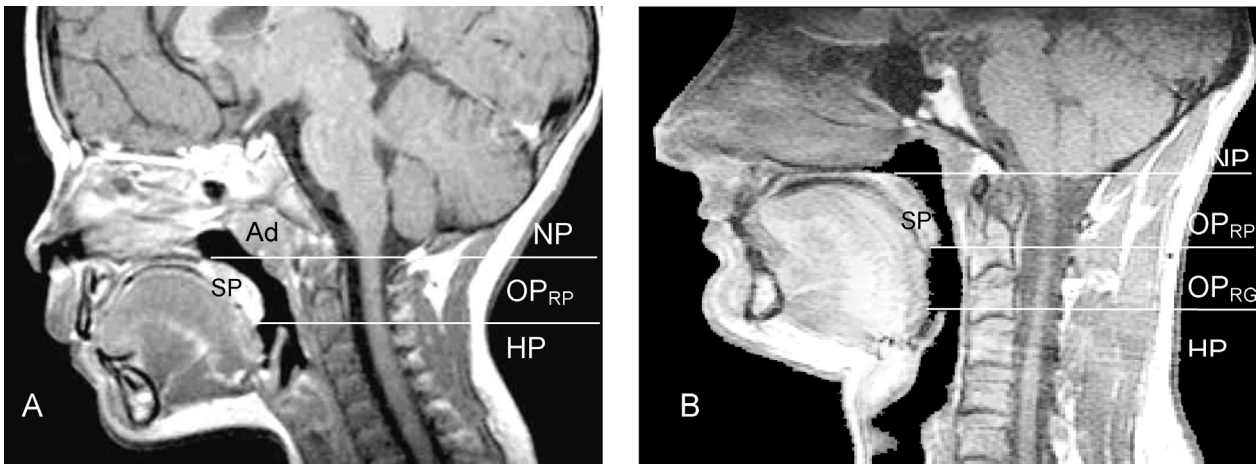

Fig. 1. Anatomy of the pharynx. A midsagittal magnetic resonance image of the head and neck of a child (A) and an adult (B) are shown. The airway is shown in black. The radiographic anatomical regions of the upper airway in the child are the nasopharynx (NP), oropharynx adjacent to the retropalatal region (OPRP), and hypopharynx (HP). The adult airway differs from that of the child by having, in addition, an oropharyngeal segment that is retroglossal (OPRG). This anatomic difference is related to the descent of the larynx during the first 18 months of life. Ad refers to adenoid; SP, soft palate.

considerations fall into two categories: those related to upper airway structure and those related to neuromuscular function; these should not be considered independently but rather by their interactions with each other and other anatomic and physiological phenomena during growth and development.

3. Pathophysiological mechanisms of OSAS

The human upper airway is a collapsible space whose shape is formed by its surrounding anatomic structures and tissues. It participates in three main functions: respiration, deglutition and speech. Each function has differing requirements – speech and deglutition benefit from the pliable nature of the airway but respiration, particularly during sleep, is better served by a stiffer airway that preserves patency. The pharynx is divided into 3 sections: (1) the nasopharynx, which extends from the choanae anteriorly and lies above the plane of the soft palate; it connects to the nasal cavity via the choanae, (2) the oropharynx, which lies between the level of the soft palate and the larynx inferiorly and communicates with the oral cavity anteriorly divided into a retropalatal portion bounded by the soft palate anteriorly and a retroglossal portion bounded by the posterior portion of the tongue anteriorly, and (3) the hypopharynx which lies posterolateral to the larynx (Fig. 1). Developmentally, the human uvula and epiglottis are in close proximity at birth creating a more secure airway, but by about 18 months of age, the larynx descends to the level of the fifth cervical vertebra resulting in a more collapsible airway with a prominent retroglossal oropharynx (Fig. 1) (Arens and Marcus, 2004).

The pharynx can be modeled as a Starling resistor representing a collapsible segment bounded by rigid segments upstream (nasal cavity) and downstream (trachea) (Arens and Marcus, 2004). The Starling resistor model predicts that, under conditions of flow limitation, inspiratory airflow is determined by the pressure changes upstream (nasal) to the collapsible portion of the upper airway and is independent of the downstream (tracheal) pressure generated by the diaphragm. Collapse occurs when the pressure surrounding the collapsible segment of the upper airway, known as critical tissue pressure (Pcrit), becomes greater than the pressure within the collapsible segment of the airway and when upstream pressure is lower than Pcrit resulting in airway obstruction with reduced or absent air flow. When Pcrit is approximately equal to airway pressure, airway structures flutter as air passes intermittently through the pharynx, generating snoring sounds. Upstream pressure can drop when nasal resistance is increased as in craniofacial abnormalities. Of note, Pcrit depends on neuromuscular activation in addition to the passive tissue properties of the airway because the pharynx is not merely a passive tube, it also contains active musculature (Arens and Marcus, 2004). As an example, in an anatomically compromised child with OSAS due to adenotonsillar hypertrophy, the upper airway is kept open while awake by muscular activation that compensates for the narrow airway anatomy that predisposes to collapse; but during sleep this compensation may be lost resulting in airway obstruction.

3.1. Anatomical considerations

Anatomic determinants of OSAS in children can be discussed in relation to broad age categories – infants, children and adolescents.

3.1.1. Infancy

Infants are predisposed to obstructive events and desaturation during sleep because of high nasal resistance and reduced airway stiffness (Arens and Marcus, 2004; Katz et al., 2012). In addition, a highly compliant chest wall with reduced functional residual capacity in infants results in lower oxygen content in their lungs and predisposition to desaturation when ventilation is impaired by upper airway obstruction. Mere spontaneous flexion of the neck can also result in airway obstruction in premature infants (Thach and Stark, 1979). Also, only a minority of infants switch to oral breathing after nasal occlusion (Swift and Emery, 1973) and therefore obstruction of the nasal passages from respiratory infection, craniofacial syndromes or choanal stenosis can result in significant OSAS. Upper airway obstruction may also occur in infancy as a result of laryngospasm and airway edema from gastroesophageal reflux.

OSAS in infancy is notable for its association with craniofacial anomalies and conditions causing soft tissue enlargement. Craniofacial abnormalities are seen with single gene disorders such as Crouzon and Apert syndrome that cause premature fusion of skull bones and with chromosomal abnormalities such as Down syndrome that lead to abnormal facial bone development. Mechanisms for airway obstruction with craniofacial abnormalities include increased upper airway resistance with maxillary hypoplasia and choanal stenosis or compromised pharyngeal space with mandibular hypoplasia. Soft tissue enlargement, including relative or absolute enlargement of the tongue, can compromise airway size in infants in disorders such as Down syndrome and Weidman-Beckwith syndrome. In infants older than 6 months of age, adenotonsillar hypertrophy, especially adenoidal hypertrophy

can result in severe OSAS with failure to thrive that resolves after adenotonsillectomy. Laryngomalacia or weakness of the larynx is another condition characteristically seen in infants that can result in upper airway obstruction and OSAS that often improves after surgical intervention in the form of supraglottoplasty (Zafereo et al., 2008).

Neurological conditions such as static injury to the brain (cerebral palsy) and developmental abnormalities of the cranial nerve nuclei innervating the pharyngeal musculature such as Moebius syndrome can result in lower muscular tone in the upper airway in infants predisposing them to upper airway obstruction. Interestingly, Down syndrome predisposes to OSAS with a convergence of smaller bony structure, larger soft tissues and lower airway tone.

Of note, many of these conditions such as Crouzon and Apert syndromes, Down syndrome and cerebral palsy can also cause OSAS in older age groups. Overall, OSAS in infancy has not been extensively studied and the incidence of OSAS is not known. Limited information is available regarding the physiological effects of OSAS in infants except for the observation of extreme morbidities such as failure to thrive or cor pulmonale (Brouillette et al., 1982).

3.1.2. Childhood

Anatomical factors contributing to OSAS in childhood can be discussed in terms of location of obstruction, soft tissue enlargement and craniofacial structure. The location of maximal upper airway narrowing in children is usually at the level of the adenoid and soft palate based on endoscopic and MRI data (Arens and Marcus, 2004). The airway is narrowest at the level of the "overlap region" where the adenoid overlaps the lingual tonsils in the upper two thirds of the pharynx (Fig. 2) (Arens et al., 2003). Adenotonsillar tissues grow commensurate with age in children without OSAS and maintain a constant proportionality with the pharyngeal airway (Arens and Marcus, 2004). It has been speculated that disproportional overgrowth of the adenoid and tonsils in children with OSAS results from inflammation and/or infections but the mechanisms leading to this process have not been elucidated. Adenotonsillar size is greater in children with OSAS, but only weakly correlated with OSAS severity, and position and orientation of these tissues may be important to causation of airway obstruction. Removal of adenoids and tonsils results in improvement of OSAS in approximately 85% of children with OSAS and adenotonsillar hypertrophy, but the rest continue to have some degree of obstruction indicating the importance of other factors in childhood OSAS.

Other soft tissues have not been implicated in the causation of OSAS in childhood. The tongue, the largest soft tissue structure around the pharynx, has been reported to be similar in size in children with OSAS and in controls. The soft palate is increased in size with OSAS, but the difference in size is not large enough to contribute to OSAS and the enlargement is probably secondary to inflammation from snoring (Arens et al., 2001). The evidence regarding craniofacial structures causing OSAS in childhood is mixed. Studies using cephalometrics suggest that minor differences in anatomy such as retrognathic mandibles and increased craniomandibular, intermaxillary and mandibular plane angles which indicate a divergent growth pattern may be promoting SDB. However, other investigators have reported mild changes and reversibility after adenotonsillectomy suggesting these are effects of OSAS rather than causations. MRI evaluation of the mandibular, maxillary and palatal dimensions has not revealed smaller dimensions in children with OSA suggesting that these do not contribute to OSAS in children without craniofacial syndromes (Arens and Marcus, 2004).

Obesity in childhood has now become a recognized contributor to pediatric OSAS with the arrival of the epidemic of childhood obesity; national estimates of obesity in children are 12% and 18% at ages 2–5 years and 6–11 years respectively (Ogden et al., 2012). Epidemiologic evidence suggests that obesity increases the odds of OSAS by 4.5 (Redline et al., 1999) and children with obesity have smaller adenotonsillar tissue size for a similar degree of OSAS (Dayyat et al., 2009), even though adenotonsillar hypertrophy continues to be a significant factor in obese children with OSAS (Arens et al., 2011). Factors that potentially lead to OSAS in children with obesity include deposition of adipose tissue in fat pads and soft tissue around the pharynx resulting in limitation of airway size, reduction of functional residual capacity because of impingement of lung volume by increased abdominal contents (with consequent reduction of oxygen reserves and predisposition to hypoxemia) and diminution of ventilatory drive seen with obesity. In addition, reduced lung volume can decrease airway stiffness by reducing tracheal tethering and thus may increase the propensity for airway collapse during sleep. Finally, the weighing down of the chest wall with obesity and consequent reduction in compliance may lead to increased work of breathing and hypoventilation that can predispose to airway collapse during sleep when ventilatory drive is potentially diminished (Arens and Marcus, 2004; Dayyat et al., 2009).

3.1.3. Adolescence

The prevalence of OSAS in adolescents has not been widely reported but the prevalence of OSAS in obese adolescents is high, ranging from 19% to 32% (Verhulst et al., 2007; Wing et al., 2003). Obesity is seen in 18.4% of adolescents in the U.S.A. (12–19 years age) (Ogden et al., 2012) and is a major contributor to OSAS in this age group. Adenotonsillar hypertrophy is associated with OSAS in older children and adolescents (Verhulst et al., 2007; Wing et al., 2003), but the resolution of OSAS after adenotonsillectomy in obese children is limited (Mitchell and Kelly, 2004) suggesting the role of other contributors such as obesity and functional factors. Comparison of obese adolescents with and without OSAS in a recent study showed larger adenoids, tonsils and retropharyngeal lymph nodes in the OSAS group but no difference in tongue or mandible size. Neck parapharyngeal fat and visceral adiposity was greater in OSAS adolescents but did not correlate with degree of OSAS, perhaps due to a smaller sample size or because of association only with severe OSAS. Interestingly, lymphoid tissue size did not correlate with BMI z-score suggesting that lymphoid hypertrophy was not secondary to obesity alone and occurred due to a separate etiological factors such as a different obese phenotype (Arens et al., 2011).

3.2. Functional considerations

There are several arguments that suggest that functional attributes have an important role in limiting OSAS in children. The first is based on the fact that the upper airway in children is smaller compared to adults. Since the prevalence of OSAS is much lower in children, it is probable that children have non-anatomical attributes that enhance airway stability during sleep. The second is based on the fact that airway obstruction occurs during sleep and not during wakefulness, implying that neuromotor activation keeps the airway open during wakefulness but not during sleep when activation is diminished. The third is based on the fact that subjects with OSAS survive each night. Therefore, there must be overriding mechanisms that prevent unremitting airway obstruction and anoxia from leading to death.

3.2.1. Central ventilatory drive

The central ventilatory drive changes with age from infancy to adulthood. While methodological limitations in measuring drive, and mechanical and anatomical differences across the age spectrum do not allow precise comparisons of ventilatory drive across the life span, it appears that ventilatory drive gradually declines from infancy to advanced age. This decline is thought to be because

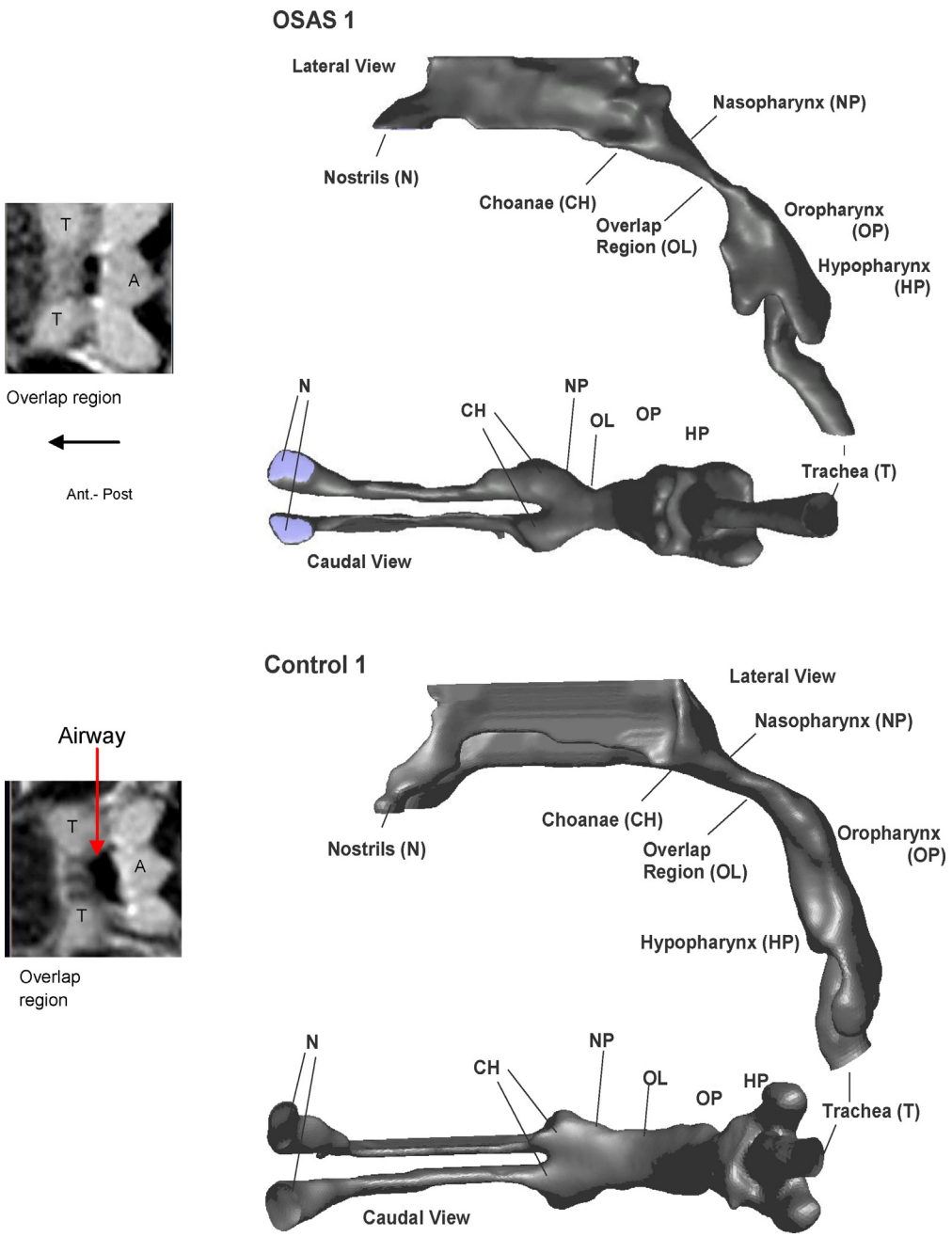

Fig. 2. Adenoid and tonsils overlap region. Lateral and caudal views of magnetic resonance imaging reconstruction of the upper airway of a child with obstructive sleep apnea syndrome (OSAS 1) and a control child (Control 1). The region of maximal narrowing in both subjects is the regions where the adenoid overlaps the tonsils (overlap region OL); this is more severely restricted in the OSAS subject. Inserts include images perpendicular to the airway in the overlap region; adenoid (A), tonsils (T).

of declining basal metabolic rate with age. The central ventilatory drive facilitates upper airway muscle dilation and reduction in ventilation leads to a compensatory increase in ventilatory drive. Central ventilatory drive, compensatory gain of ventilation in response to hypoventilation and airway tone can interact with each other in the setting of compromised airway anatomy to result in varied phenotypes of OSAS. Thus, a lower ventilatory drive would lower the amount of anatomic compromise necessary to cause hypoventilation or some subjects with OSAS may have greater reduction in airway tone with intrinsic fluctuations of respiratory drive (Series et al., 1989; Wellman et al., 2013). Compensatory ventilatory gain can also play a role in airway obstruction – a low compensatory gain in response to hypercarbia can result in perpetuation of hypoventilation induced by upper airway obstruction or, a high compensatory gain can result in widely fluctuating responses to hypoventilation (from upper airway obstruction) causing ventilatory instability and upper airway tone variability that facilitates airway obstruction (Arens and Marcus, 2004; Wellman et al., 2004). The data regarding ventilatory drive and response to hypoxia and hypercarbia in children are limited. Non-obese children with OSAS have normal ventilatory responses to hypoxia and hypercapnia (Arens and Marcus, 2004). This could be due to the shorter lifetime exposure to OSAS effects, fewer associated co-morbidities, or due to an intrinsic difference in pathophysiology of OSAS in children as compared to adults. However, subtle changes such as lack of a consistent ventilatory response to hypercapnia in the early morning and association with airway collapsibility with reduced ventilatory drive during sleep may be seen in children (Arens and

Marcus, 2004). In obese adolescents, a recent study reported a reduced ventilatory response to hypercapnia during sleep but this has not been confirmed by other studies (Yuan et al., 2012).

3.2.2. Ventilatory response to inspiratory loading

During wakefulness, addition of an external resistive load leads to an immediate compensatory increase in ventilatory effort that maintains gas exchange. In sleep, this compensatory response is not normally seen unless there is a complete airway occlusion. With partial occlusion, a decrease in minute ventilation ensues and compensation of ventilation is delayed; this eventual correction is believed to be in response to gas exchange abnormalities. In normal children, this compensation can be limited and delayed by 3 min or more as compared to adults (Marcus et al., 1999). Children with OSAS have reduced arousal responses to inspiratory resistive loads during sleep that together with the aforementioned inadequate compensation of ventilation may explain the prolonged periods of obstructive hypoventilation observed in childhood OSAS (Arens and Marcus, 2004).

3.2.3. Arousals

Arousals are a normal phenomenon of sleep and are defined as sudden shifts in EEG frequency lasting for 3 s. However, if arousals occur too often they produce sleep disruption and interfere with the restorative nature of sleep. It should also be pointed out that arousals may be protective to subjects with OSAS since they coincide with increased dilator muscle activity, reduced upper airway resistance, and restoration of normal ventilation.

Studies in children and adults have clearly shown that frequent arousals and sleep fragmentation often lead to decreased vigilance, sleepiness and other neurocognitive impairments. Interestingly, children are much less prone to arousals due to respiratory events than adults and typically are less sleepy compared to adults with OSAS. The major stimuli for arousals from OSAS are thought to be mechanical stimulation of lung and chest wall stretch receptors due to increased respiratory effort. However, hypercapnia is also considered a potent arousal stimulus. The majority of obstructive events in adults are associated with arousals from non-REM sleep. In children the majority of obstructive events occur during REM sleep, and associated arousals are less frequent than in adults. Normal children have a higher arousal threshold than adults; children with OSAS seem to have an even higher threshold for arousal in response to inspiratory loading (Marcus et al., 1999) and hypercapnia (Marcus et al., 1998b) compared to children without OSAS.

3.2.4. Neuromotor tone

Flow through the upper airway depends not only on mechanical and anatomic factors but also the active dilation of the airway by neuromotor tone. Of note, this active dilation is closely integrated with ventilatory drive and compensatory ventilatory responses as discussed in Section 3.2.1. Pressure flow relationships based on the Starling model provide an understanding of airway stability in the "active" state with neuromotor activation and in the "passive" state before neuromotor responses are activated. Plotting a range of airway pressures against the resulting maximal inspiratory flows of breaths generates a pressure flow line with the critical closing pressure (Pcrit) being represented by the intercept on the pressure axis. Airway pressure is applied by a nasal mask with the subject in a supine position and airflow is measured by a pneumotachometer; the pressures employed span a range of positive to negative (subatmospheric) values. When pressure is maintained in a steady state, neuromotor activation occurs and the airway is in the "active" state; this active Pcrit is considered a measure of airway collapsibility (Figs. 3 and 4). The airflow in the first few breaths following a sudden drop in pressure, before neuromotor responses can occur, represents the "passive" airway;

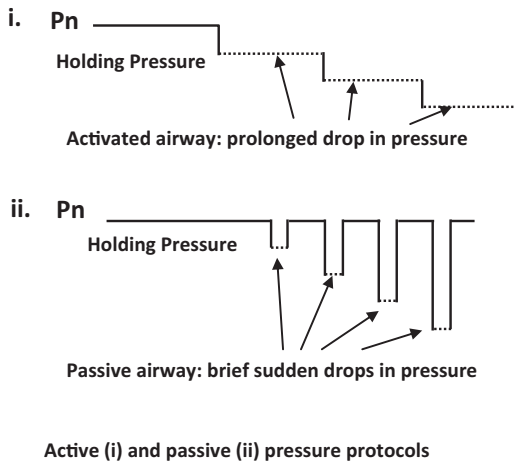

Fig. 3. Active and passive critical closing pressure protocols. Schematic of active and passive airway critical closing pressure protocols. Holding pressure (horizontal sold line) is maintained at levels just enough to abolish flow limitation. (i) To determine active critical airway closing pressure, nasal pressure (Pn) is reduced in 1–2 cm H_2O decrements (broken lines) and maintained for prolonged periods (1–10 min) to allow dynamic airway activation to occur and maximal inspiratory air flow is obtained at each pressure. Airway pressure is reduced until airflow approaches zero or arousal from sleep occurs. (ii) To determine passive airway critical pressure, pressure drops (broken lines) from holding pressure (horizontal sold line) are made for brief periods lasting 5 breaths, before dynamic responses are activated. Airway pressure is then raised to holding pressure rapidly for 1 or more minutes before dropping it further in increments of 1–2 cm H_2O pressure till zero flow is approximated or arousal occurs. Maximal inspiratory flow (Vi max) at each pressure setting is determined. Pressures employed span a range of positive to negative (subatmospheric) values to estimate critical closing pressure.

this passive Pcrit estimates mechanical and structural properties of the airway (Figs. 3 and 4). The nasal pressure at which the airway closes or is estimated to close by the pressure-flow line is typically lower for the active airway compared to the passive airway (Fig. 4). In children, the Pcrit tends to be very negative (because motor tone is very high) such that the slope of the pressure flow line approaches zero and extrapolation of the line becomes unreliable (Fig. 4). As a result, the slope of the pressure flow line is taken as the next best estimate of upper airway collapsibility. The passive airway closing pressure can also be estimated by the pressure-cross

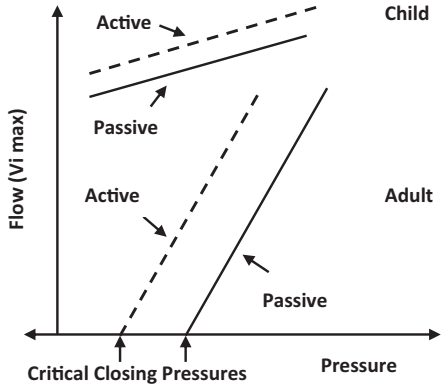

Fig. 4. Pressure flow relationship and critical closing pressure. Schematic representation of plots of nasal pressure (on *x*-axis) and air flow (Vi max) (on *y*-axis). Pressure flow lines are calculated from flow at each pressure setting in the active and passive conditions to obtain critical closing pressures; the intercept on the *x*-axis is the critical closing pressure. The activated pressure flow line (dashed line) has a lower airway closing pressure than the passive airway pressure flow line (solid line). Children tend to have very stable airways with a minimal slope and a much lower closing pressure (dashed and solid lines at top) compared to adults (dashed and solid lines below).

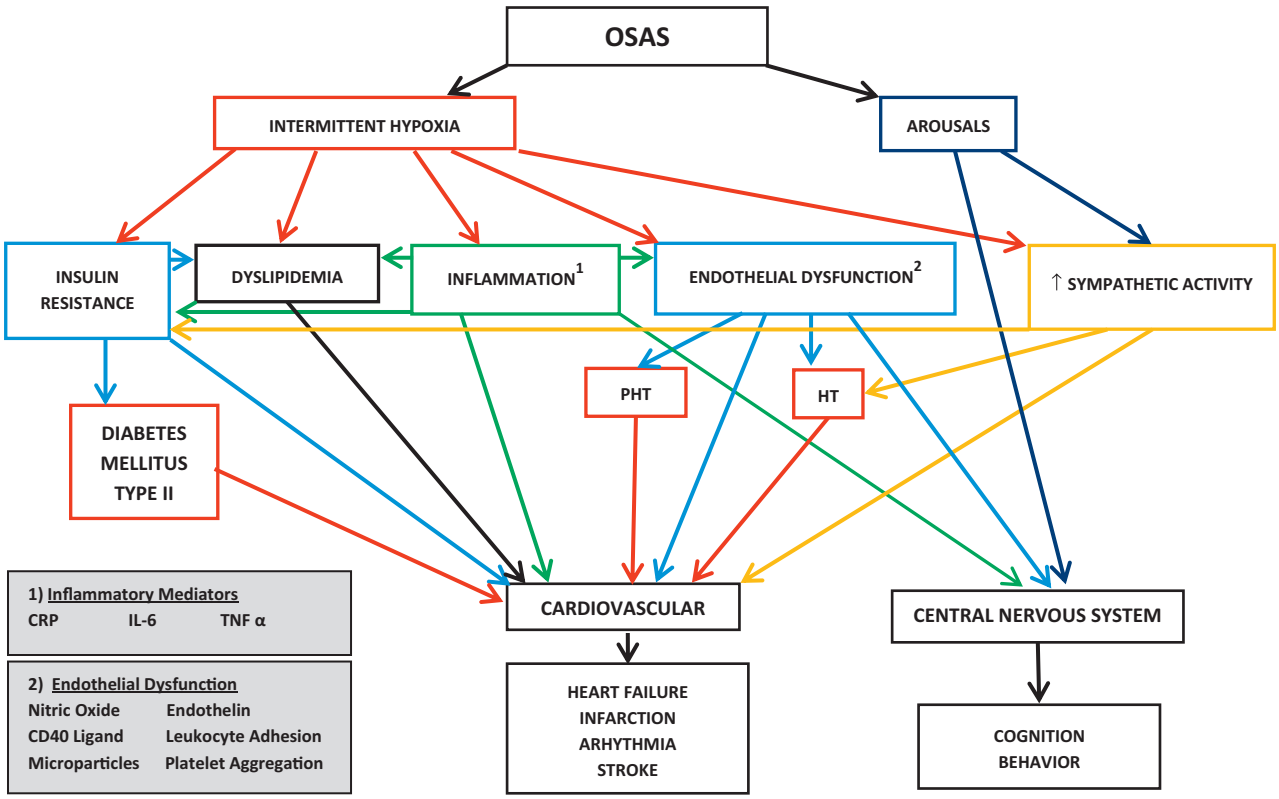

Fig. 5. Physiological effects of OSAS. Schematic of the complex mediation of pathophysiological effects of OSAS affecting metabolic, cardiovascular and neurocognitive function. Examples of (1) inflammatory mediators and (2) endothelial dysfunction mediators that may contribute to the pathophysiological effects of OSAS are displayed in shaded boxes. Note that genetic factors such as Apolipoprotein E ε4 allele and TNF α 308 G/A polymorphism contribute to mediation of effects of OSAS. PHT refers to pulmonary hypertension and HT to systemic hypertension.

sectional area relationship endoscopically observed in anaesthetized subjects (in whom neuromotor activation is suppressed) analogous to the pressure–airflow relationship. Neuromotor activation can more directly be estimated by measuring the EMG activity of the genioglossus muscle which is the major pharyngeal dilator.

The pediatric airway is very resistant to collapse compared to the adult airway; airway collapsibility increases with age during adolescence and is not a function of pubertal development. In children and adolescents with OSAS the critical closing pressure is much higher than in non-OSAS children (Arens and Marcus, 2004; Huang et al., 2012). Childhood OSAS is most prominent in REM sleep which is associated with reduced pharyngeal tone and wide fluctuations of airflow, both of which can contribute to OSAS. While closing pressure is difficult to measure in REM sleep for practical reasons, reduced airway tone can be demonstrated by EMG studies of the tongue muscles. Awake children with OSAS have higher baseline EMG tone than normal children most probably to compensate for their narrower airways. With sleep onset these children have a rapid decline in EMG tone (Katz and White, 2003) with a further decline in REM sleep, predisposing them to further airway obstruction (Katz and White, 2004).

4. Measurement of OSAS

The previous sections have considered anatomical and functional determinants of OSAS, but the actual quantification of OSAS is currently performed by polysomnography. A brief summary of polysomnography is presented here, a more detailed discussion is available elsewhere (Muzumdar and Arens, 2008).

4.1. Polysomnography

Polysomnography is performed overnight in a sleep laboratory with measurement of multiple parameters that capture sleep characteristics and respiratory events.

4.2. Recording of sleep and sleep disruption

Electroencephalography (EEG), electro-oculography (for eye movements) and submental electromyographic activity allow sleep staging and arousal detection. Arousals are scored when there are abrupt shifts in EEG frequency, not including spindles, that last at least 3 s (Iber et al., 2007a). Arousals may be spontaneous or may be related to technician interventions, respiratory events or limb movements and normative data in children have been published (Muzumdar and Arens, 2008).

4.3. Recording of respiratory events

The sensors for detection of airflow are the oronasal thermal sensor, nasal air pressure transducer, capnograph (to measure exhaled CO_2), and calibrated inductance plethysmography of chest and abdomen. In addition, respiratory effort is determined by inductance plethysmography. Blood oxygen saturation is measured by pulse oximetry and alveolar ventilation by transcutaneous or end-tidal CO_2 monitoring (Iber et al., 2007b). Respiratory events are briefly reviewed here and usually reported as the respective indices (number of events/hour of sleep).

Obstructive apnea: Scored when there is a ≥90% drop in the signal amplitude of airflow and the event lasts for at least 2 breaths with continued inspiratory effort (Iber et al., 2007b).

Mixed apnea: Scored if the airflow signal meets duration and amplitude criteria for obstructive apnea, and an initial absent inspiratory effort is followed by respiratory effort during the event (Iber et al., 2007b).

Central apnea: Scored when the respiratory event is associated with absent inspiratory effort throughout the event with one of the following: (1) event lasts >20 s or (2) event lasts at least 2 missed breaths and is associated with an arousal, an awakening or a ≥3% desaturation (Iber et al., 2007b).

Hypopnea: Scored if there is ≥50% drop in airflow signal amplitude and the event lasts at least 2 missed breaths with an associated arousal, awakening or ≥3% desaturation (Iber et al., 2007b).

Respiratory effort related arousal (RERA): A RERA can be scored when an arousal is preceded by snoring, noisy breathing, or visual evidence of increased work of breathing (Iber et al., 2007b).

Hypoventilation: Sleep related hypoventilation may be scored when >25% of the total sleep time is spent with a CO_2 >50 mm Hg, measured by transcutaneous PCO_2 and/or end-tidal CO_2 sensors (Iber et al., 2007b).

The parameters that are used to summarize sleep disordered breathing include the obstructive apnea index, apnea hypopnea index and hypoventilation (as defined above). In addition, oxygen desaturation index (number of 3% or more desaturations/hour), duration of oxygen saturation below 90% and oxygen saturation nadir are also reported. Sleep quality is summarized by arousal index, respiratory arousal index (RERAs) and sleep efficiency (sleep time/sleep opportunity. Most authorities agree that an obstructive apnea index >1 event/h, and/or obstructive apnea-hypopnea >2 events/h are sufficient for the diagnosis of OSAS (Redline et al., 2011).

5. Physiological effects of OSAS

5.1. Neurobehavior and neurocognition

The most important neurological impairments described in children within the spectrum of obstructive sleep disordered breathing, including OSAS and PS, are neurobehavioral and neurocognitive deficits. For a comprehensive review on the topic the reader is directed to the review by Beebe, which also includes methodological aspects (Beebe et al., 2003).

5.1.1. Neurobehavior

The main neurobehavioral impairments in children fall within three categories:

(a) *Behavior regulation and inattention*: Hyperactivity, rebelliousness, and aggression are the most consistent behavior patterns reported by parents (Chervin et al., 2002). Inattentive behaviors have also been reported, however, most studies do not allow for the differentiation of impulsiveness and inattentiveness.
(b) *Mood and emotional control*: Most studies based on parental report do not suggest that children with SDB have significant mood disorders despite internalizing behaviors. However, two reports using more direct measures, suggest that anxiety and depression may be more common in these children (Owens et al., 2000; Stein et al., 2001). These findings are also supported by the fact that emotional instability has been shown to be increased in SDB compared to controls and there is a good correlation between mood disorders and emotional control (Rosen et al., 2004).
(c) *Sleepiness*: Sleepiness is one of the most important neurological consequences of SDB. It affects both behavior and cognition and is considered to result from the impact of sleep disruption and sleep loss in these subjects. In contrast to adults, children with SDB do not usually complain of daytime sleepiness. However, objective measures of sleep propensity such as the multiple sleep latency test (MSLT) (Gozal et al., 2001), and the sleep pressure score (Tauman et al., 2004) suggest that children with SDB are sleepier than controls.

5.1.2. Neurocognition

Results of neurocognitive and psychomotor function tests in children with SDB have been variable. Several studies that addressed the most important domains of these functions including intelligence, executive function, motor function and vigilance suggest that these are impaired in children with SDB (Gottlieb et al., 2004; O'Brien et al., 2004). However, other studies do not support impairments in all domains. In addition, there is concern that many studies have insufficient methodological rigor to support the validity of their conclusions. However, important evidence of the negative impact of SDB on neurocognitive function in children is the consistency of reports showing poor academic achievements in these children, including those with mild forms of SDB and in those with PS. These studies also document that younger children are more affected than older ones (Urschitz et al., 2003).

Though the precise mechanisms and/or genetic susceptibility for these impairments are still unknown, possible mechanisms supported by animal models include sleep fragmentation and sleep loss in addition to intermittent hypoxia that precipitates endothelial dysfunction via inflammatory changes (Fig. 5). Evidence of neuronal injury in children with severe OSAS has been demonstrated by proton magnetic resonance spectroscopic imaging raising concerns that these changes may not be completely reversible (Halbower et al., 2006). Other studies suggest that injury could be more prominent in genetically susceptible populations such as those carrying the ε4 isoform of apolipoprotein E allele (ApoE4) and in younger children during synaptic development (Lal et al., 2012).

5.2. Cardiovascular system

Epidemiologic evidence from prospective studies in adults has established that OSAS is associated with an increased incidence of cardiovascular diseases such as coronary disease, stroke, and heart failure (Monahan and Redline, 2011). Here we summarize the evidence of cardiovascular compromise that has been demonstrated in children including blood pressure regulation and myocardial function and the mechanisms that underlie these changes including endothelial dysfunction, autonomic imbalance and inflammation (Fig. 4).

5.2.1. Hypertension

OSAS has been associated in adults with elevated blood pressure (BP) in the pre-hypertensive and hypertensive range and with resistant hypertension (Monahan and Redline, 2011). Systemic hypertension is a clinically significant morbidity because it is one of the pathways that can lead to end-organ damage and cardiovascular morbidity associated with OSAS. Hypertension in OSAS has been causatively linked primarily to increased sympathetic output from arousals and oxygen desaturations (Fig. 4). More recently, reduced slow wave sleep was associated with OSAS mediated hypertension in an adult epidemiologic study and this interesting association was putatively linked to a diminution of the normal reduction in sympathetic tone during slow wave sleep (Monahan and Redline, 2011).

In children, the link between systemic hypertension, particularly systolic blood pressure, and OSAS is not as strong but definitive evidence of diastolic hypertension and dysregulation of BP has been presented. In an early study Marcus et al. compared BP measured by an automated system, using appropriately sized arm cuffs, in a small sample of children with OSAS to children with PS. They noted

higher diastolic BP during sleep and wake in children with OSAS with an apnea hypopnea index of 16 ± 15 events/h and differences in diastolic BP were correlated with respiratory events suggesting a causal link (Marcus et al., 1998a). They did not find differences in systolic BP, but this study was limited by a small number of subjects that were not closely matched in terms of age and sex distribution. Also, it is not clear if a more uniform set of children with higher levels of respiratory disturbance would have demonstrated increased systolic BP. A more recent prospective study with a larger number of subjects that included children without SDB found higher BP, diastolic and mean arterial pressure, and to a lesser extent systolic BP during wake and sleep (Horne et al., 2011). The methodology of this study was different in that BP was measured by photoplethysmography which measures BP from optical estimates of fingertip volume. Of note, they reported no significant differences in BP in the between children with PS and mild to moderate OSAS defined as an AHI of 1–5 and > 5 events/h respectively. It is possible that at a significantly higher threshold of AHI the effects of OSAS would be more prominent and result in an increase in systolic BP that is not seen at lower levels of OSAS.

What is the evidence regarding OSAS and BP regulation in children? In a prospective study utilizing ambulatory 24 h blood pressure monitoring, Amin et al. found increased diastolic BP similar to that observed by Marcus et al. in children with OSAS (Amin et al., 2004). Diastolic BP was shown to increase in a dose dependent fashion in three groups of SDB of increasing severity – (1) PS, (2) children with "mild" OSAS (AHI between 1 and 5 events/h), and (3) "moderate" OSAS (AHI > 5 events/h). In addition, they reported evidence of dose dependent BP dysregulation in the form of increased BP variability and reduction of the physiologic nocturnal dipping of BP, both phenomena that are considered precursors of systemic hypertension. All of the above raise concern regarding long term cardiovascular morbidity associated with childhood OSAS as these children enter adulthood.

5.2.2. Cardiac dysfunction

Heart failure risk is higher in adults with OSAS similar to the risk of hypertension, but in children overt heart failure in conjunction with OSAS is only occasionally reported, usually in the context of pulmonary hypertension (Amin et al., 2002). The data regarding the effects of OSAS on cardiac function in the majority of children with OSAS are more subtle and can be discussed in terms of effects on the left and right side of the heart.

Amin et el demonstrated that OSAS is associated with increased left ventricular mass in a dose dependent fashion (with increasing apnea hypopnea index) and speculated that this effect was mediated by intermittent hypoxia rather than via hypertension because blood pressure was not significantly higher in children with OSAS (Amin et al., 2002). The same group also investigated the effect of OSAS on left ventricular function and reported impaired left ventricular function in children with OSAS, again in a dose dependent manner (Amin et al., 2005). They could not find direct evidence of diastolic dysfunction due to greater left ventricular mass which could be due the power of the study or due to myocardial dysfunction directly from hypoxia. These findings of left ventricular abnormalities are by themselves subtle but have been shown to be associated with poorer long term outcomes in adult studies and are therefore worth noting.

Clinically, several reports have associated OSAS in children with pulmonary hypertension and right heart failure. However, studies with direct measurements of right ventricular function in children with OSAS are limited. Based on radionucleotide ventriculography Tal and colleagues showed that OSAS was associated with right ventricular dysfunction that improved after relief of obstruction (Tal et al., 1988). Amin et al. reported a higher likelihood of right ventricular dimensions with an apnea–hypopnea index of more than 10/h and speculated in a subsequent publication that pulmonary hypertension may be secondary to impaired left ventricular filling (Amin et al., 2005). Taken together, these studies provide evidence of cardiovascular dysfunction in children that may provide insight into the long term morbidity that can be attributed to OSAS.

5.3. Autonomic nervous system

The effects of OSAS on cardiovascular functions are thought to be at least partially attributable to perturbation of the autonomic nervous system (ANS). ANS function has been studied invasively in adults by measuring muscle sympathetic nerve activity. These studies have demonstrated increased sympathetic output in subjects with OSAS compared to controls (Narkiewicz and Somers, 2003). In children, however, noninvasive methods that estimate autonomic function are more appropriate and have therefore been used to study ANS responses in children with OSAS.

Heart rate variability (HRV) is a noninvasive method that can estimate autonomic balance. HRV analysis estimates sympathetic to parasympathetic balance by calculating the ratio of low-frequency to high-frequency band power extracted from electrocardiographic recordings by methods such as fast Fourier transformation. High frequency power is related to parasympathetic activity while low frequency power is related to both sympathetic and parasympathetic activity and the ratio of low to high frequency power (LF/HF) is dependent on the balance of sympathetic to parasympathetic activity. An increase in LF/HF represents tilting of the autonomic balance toward the sympathetic component and has been clearly demonstrated in children with OSAS as in adults (Fig. 5) (Baharav et al., 1999). Pulse arterial tonometry is a noninvasive technique for detecting sympathetic vasomotor tone in peripheral vessels using a finger plethysmograph. An increase in sympathetic activity results in vasoconstriction that is detected by attenuation of the tonometry signal on the plethysmograph. This attenuation was demonstrated to be greater in children with OSAS by O'Brien et al. providing further evidence of sympathetic over activity in children with OSAS. Finally, biochemical correlates of increased sympathetic activity appear to confirm the presence of OSAS severity-dependent increases in the form of higher levels of urinary catecholamines especially, norepinephrine (Snow et al., 2009).

Sympathetic over activity in OSAS is believed to be mediated by the stimulation of peripheral arterial chemoreceptors by hypoxemia that results in increased sympathetic efferent traffic during hypoxemic episodes (Fig. 5). In addition, respiratory events during sleep such as apnea/hypopnea interrupt lung inflation which is associated with physiologic sympathetic inhibition by vagal circuits resulting in greater sympathetic traffic. Lastly, arousals resulting from OSAS may also induce increased sympathetic output via cortical inputs (Fig. 5) (Muzumdar and Arens, 2012).

Autonomic function can also be estimated by baroreflex sensitivity (BRS), which evaluates the baroreflex function of the ANS. Baroreceptors are mechanoreceptors in the carotid sinus and aortic arch that relay changes in arterial wall stretch to control centers in the brainstem from where autonomic outflow is modulated, producing changes in cardiovascular variables such as heart rate, heart contractility and vasoconstriction to maintain homeostasis. The decrease/increase in heart beat interval in response to reduction/increase respectively in arterial blood pressure provide a measure of BRS. BRS can be measured in the temporal and frequency domains and impairment in BRS has been associated with an increased risk of developing hypertension and cardiovascular disease in that a central remodeling of autonomic cardiovascular control may precede the development of daytime hypertension. McConnell et al. reported impaired BRS parameters in temporal and frequency domains in children with OSAS having more than

5 apnea hypopnea events/h (McConnell et al., 2009). Normal respiratory drive, baroreceptor sensitivity, and sympathetic discharge are closely related. Baroreflex suppression with OSAS may lead to reduction in the direct inhibition of sympathetic discharge by the baroreceptor stimulation, in turn leading to sympathetic predominance, particularly at the respiratory frequency. It is also possible that sympathetic activation with OSAS may alter the afferent regulation of the baroreflex response.

An important issue regarding ANS dysfunction and OSAS is the reversibility of the dysfunction after resolution of OSAS. Animal experiments suggest that this dysfunction may persist after resolution of sleep apnea. Studies in children looking at changes 6 months after adenotonsillectomy indicate that autonomic dysfunction estimated by LF/HF ratio and BRS substantially improve, but not completely and some evidence of dysfunction persists despite treatment (Crisalli et al., 2012; Muzumdar et al., 2011). These persistent changes may be related to inadequate resolution of OSAS or duration of follow up but certainly merit concern regarding their potential to contribute to long term cardiovascular morbidity.

5.4. Inflammation

Similar to ANS dysfunction, inflammation and risk factors for atherogenesis provide causal pathways that link OSAS to the morbidities associated with OSAS (Fig. 5). In this context, a brief overview of atherosclerosis and cellular mediation of inflammation is discussed.

Atherosclerosis is now considered to be not merely a lipid storage disease, but also a chronic inflammatory process of the vascular wall. Lesions that start as fatty streaks contain foam cells which are macrophages that have ingested lipids, T-lymphocytes and smooth muscle cells. These lesions progress with apoptosis of the foam cells and smooth muscle cells, inflammation and fibrosis leading to mature plaques. Fatty streaks may also progress to unstable plaques that rupture and result in thrombosis and potentially lead to myocardial infarction or stroke. The traditional risk factors for atherosclerosis include aging, hypertension, genetic predisposition, diabetes, hyperlipidemia, obesity and smoking. Newer risk factors that have been recognized are markers of systemic inflammation such as fibrinogen, D-dimers and tissue plasminogen activator (Drager et al., 2011). The concomitant existence of these risk factors can make the determination of the risk from any one factor difficult and some morbidity from individual risk factors may occur only in the presence of other risk factors such as obesity. In addition, the mediation of inflammation and cardiovascular risk is intertwined with endothelial dysfunction and the metabolic syndrome (Fig. 5) as will be subsequently discussed.

The cellular mechanisms of these pathways are complex and the induction of transcription factors such as NF-kB by recurrent hypoxia may lead to upregulation of multiple inflammatory cytokines such as TNF-α, IL-8 and IL-6 (Fig. 5). Intermittent hypoxia can also induce a state of oxidative stress that is a potent activator of a cascade of inflammatory pathways that induce overexpression of adhesion molecules. These adhesion molecules facilitate the recruitment and accumulation of leukocytes, platelets and possibly red blood cells on the endothelium lining the vasculature. Such cellular interactions between blood cells and endothelial cells may promote endothelial cell injury (Fig. 5). Recurrent hypoxia has also been implicated as a cause of increasing levels of VLDL cholesterol by upregulation of hepatic enzymes of lipid biosynthesis and by the inhibition of lipoprotein lipase that clears lipoproteins from the circulation (Fig. 5). OSAS-induced dyslipidemia and oxidative stress, as well as hypertension and insulin resistance, can all lead to endothelial dysfunction (Fig. 5) (Drager et al., 2011). C-reactive protein (CRP) is another important marker of inflammation induced by oxidative stress that is secreted primarily by the liver but also by other cell types that is implicated in this complex scenario of OSAS-induced morbidities. CRP is an acute-phase reactant induced by IL-6 and is a strong predictor of coronary heart disease and of future cardiovascular events (Fig. 5). CRP promotes oxidative stress and tissue factor activation by vascular smooth muscle cells; these actions may play a crucial role in plaque instability and acute coronary syndrome. In addition, CRP levels can affect endothelial cells and induce the expression of adhesion molecules by these cells (Lavie and Lavie, 2009).

We will limit the discussion of inflammatory markers in OSAS to CRP and TNF-α as these have been well studied and provide insight into the topic. Increases in CRP have been reported in children with OSAS, particularly with a threshold of an apnea hypopnea index > 5/h, but findings have not been universal (Bhattacharjee et al., 2011; Kaditis et al., 2005). In addition, Kheirandish-Gozal et al. demonstrated a decrease in CRP levels after adenotonsillectomy in non-obese school children with OSAS together with a reduction in apnea hypopnea index from 15.6 ± 2.9 to 2.2 ± 0.8 indicating a likely causal connection (Kheirandish-Gozal et al., 2006). Thus, interacting environmental, genetic and comorbid factors may be required to produce this association. Similar to CRP, some investigators have reported increased TNF-α levels in children with OSAS, particularly with greater severity of OSAS, but other groups have not found this association, perhaps due to milder degree of OSAS studied (Bhattacharjee et al., 2011; Li et al., 2008). Interestingly, most of the increase in TNF-α has been linked to a particular single nucleotide polymorphism in the TNF-α gene demonstrating how genetic susceptibility can alter morbidity of OSAS (Fig. 5) (Khalyfa et al., 2011). Overall, evidence of systemic inflammation from OSAS in children has been demonstrated, but is likely to vary with age, genetic background, severity of sleep apnea and other concurrent clinical conditions.

5.5. Endothelial function

The physiological effects of OSAS in children and their detrimental effects on the brain and cardiovascular systems suggest that these may share common pathophysiological pathways. One of the most important potential mechanisms to mediate these end-organ effects is endothelial dysfunction, which may be linked to systemic inflammation produced by OSAS (Fig. 5) (Lavie and Lavie, 2009).

Endothelial cells maintain vascular function by promoting vasodilation, inhibiting platelet aggregation, leukocyte adhesion and smooth muscle cell proliferation. Coronary endothelial dysfunction is associated with cardiovascular events in adults and endothelial function is measured as an indirect marker of future cardiovascular events that may provide prognostic information beyond that obtained from coronary angiography or traditional clinical risk scores (Moens et al., 2005). Peripheral endothelial function is considered to be similar to coronary endothelial function and is measured to estimate coronary endothelial function. Endothelium dependent regulation of vascular tone in peripheral arteries is a commonly used test of endothelial function, usually in response to flow. Arterial caliber normally increases in response to changes in blood flow via increased shear stress that activates the mechanical receptor function of the endothelium, thus a diminished vasodilator response is evidence of endothelial dysfunction. Increased flow in peripheral arteries can be induced by occluding the artery by a cuff and abruptly releasing the occlusion. The sudden drop in resistance induces increased flow in the artery, termed reactive hyperemia and vessel diameter or time to peak flow is assessed post occlusion. This flow mediated vasodilation (FMD) measurement is affected by multiple variables such as circulating levels of estrogen, progesterone and catecholamines, diabetes mellitus, hypertension, obesity, time of day, family history of heart disease and diabetes mellitus, and cholesterol levels that need to be accounted for when

designing studies and interpreting their results. FMD can vary considerably between sessions and is more useful as a group parameter than individual marker (Moens et al., 2005).

FMD is predominantly mediated through nitric oxide (NO) dependent pathways which can be compromised by the oxidative stress that occurs as a result of repeated episodes of hypoxemia supplying NO in the endothelium. In addition, an increase in circulating levels of endogenous inhibitors of NO synthase, such as plasma nitrotyrosine and asymmetric NG-dimethylarginine (ADMA) has been demonstrated in adults with OSAS (Fig. 5) (Gozal et al., 2007b).

Impaired endothelial function has been demonstrated in adults by measuring flow mediated brachial artery dilation, with improvement after treatment of OSAS by CPAP. Gozal et al. reported analogous impairments in endothelial dependent reperfusion in non-obese prepubertal school children with OSAS (AHI = 11.9 ± 2.2) compared to controls without SDB. In that study, reperfusion normalized after adenotonsillectomy in 20/26 children (Gozal et al., 2007b). The children who did not show improvement in reperfusion were reported to have a strong family history of cardiovascular disease, a known risk factor for endothelial dysfunction, raising concern regarding early manifestations of cardiovascular morbidity in genetically predisposed subjects. The levels of plasma nitrotyrosine and ADMA were not different from children without OSAS in contrast with studies in adults, but CD40 ligand levels, a marker of endothelial dysfunction, were higher in children with OSAS (Gozal et al., 2007b). The same group has also reported the presence of circulating cell derived microparticles, biomarkers of endothelial dysfunction and myeloid-related protein 8/14, a marker of atherogenesis in children with OSAS (Bhattacharjee et al., 2012).

The association of endothelial dysfunction and OSAS in children is of greater concern in children with obesity because obesity alone has been shown to be associated with endothelial dysfunction and therefore these children may be at a higher risk for end organ injury from the combined effects of obesity and OSAS.

5.6. Metabolism

The increase in childhood obesity has brought attention to the metabolic syndrome (MS) in that age group. The MS is a constellation of pathologies that includes elements of hypertriglyceridemia, reduced high density lipoprotein (HDL) cholesterol, insulin resistance, abdominal obesity, hypertension, and the presence of pro-thrombotic and pro-inflammatory state that is associated with type 2 diabetes mellitus (DM) and cardiovascular disease (Arens and Muzumdar, 2010; Grundy et al., 2005; Lusis et al., 2008). These metabolic traits exhibit causal interactions and share common etiologies. Insulin resistance is an important component but not the sole mediator of the syndrome (Lusis et al., 2008). Insulin resistance is also a precursor to DM but this progression is thought to occur only in the subset of individuals who have an inherent predisposition to DM (Fig. 5). The Homeostasis Assessment Model (HOMA) method is usually used to assess insulin resistance from the fasting plasma insulin and glucose levels. The prevalence of the metabolic syndrome increases with the severity of obesity and may reach 50% in severely obese children (Arens and Muzumdar, 2010).

Obesity has been investigated as a cause of OSAS, but the role of OSAS as a possible cause/contributor to MS has also been studied. In addition to OSAS being causally linked to dyslipidemia, hypertension and inflammation via mechanisms such as sympathetic discharge, intermittent hypoxia and sleep fragmentation, it is also thought to mediate insulin resistance. Insulin resistance is in turn implicated in causation of dyslipidemia which is an integral part of the metabolic syndrome (Fig. 5), perhaps through increased levels of free fatty acids via reduced inhibition of lipoprotein lipase in adipocytes. Several studies in adults and obese children have shown increased levels of triglycerides, LDL cholesterol and low HDL levels that were independently associated with OSAS, but others have not found this link (Arens and Muzumdar, 2010). The mechanisms by which OSAS leads to insulin resistance are proposed to be hypoxia and increased sympathetic discharge (Fig. 5). Hypoxia has been shown to inhibit insulin receptor activation and trigger the formation of inflammatory cytokines which promote peripheral insulin resistance, while sympathetic activation induces insulin resistance by inducing glycogenolysis and gluconeogenesis (Lindberg et al., 2012).

Clinical studies in adults have implicated OSAS in the development of insulin resistance in cross-sectional and longitudinal studies. Treatment with CPAP has been reported to reduce insulin resistance in adults with OSAS (47). What is the evidence in children? Redline et al. reported increased levels of insulin (suggesting insulin resistance), blood pressure and LDL cholesterol with OSAS in a community based cohort of adolescents, an association that was independent of BMI (Redline et al., 2007). The data in pre-pubertal children also indicates an association between insulin sensitivity and OSAS in obese children, with correction of OSAS in obese children being associated with improvement in measures of insulin sensitivity and dyslipidemia. In the same study, non-obese children showed improvement in lipid profile after adenotonsillectomy but not insulin sensitivity (Gozal et al., 2008). In non-obese children, or in children with mild OSAS, the absence of an association between OSAS and insulin resistance suggests that moderate to severe OSAS might be contributing to exacerbation of insulin resistance, but may not be causing insulin resistance in the absence of obesity (Arens and Muzumdar, 2010). The concern for sleep specialists is the additive effect of OSAS in perpetuating MS in obese children, particularly with the early-starting and long term consequences of these risk factors.

6. Future directions

Several considerations arise from the varied but suggestive data that links OSAS to end organ injury in children. Some investigators point to weaknesses in the relatively low number of studies, low number of subjects in each study, and inadequate controls. Specifically, and correctly, criticisms of methodological issues such as lack of standardization of tests, lack of normal thresholds for the tests, and variations that relate to age, anthropometrics, demographics, as well as genetic heterogeneity are all valid. The important message is the call for studies that will be designed appropriately, will be adequately powered, and will be sensitive and specific to detect the neurological, cardiovascular, inflammatory and metabolic effects of OSAS in children. In addition, studies should also strive to include the use of methodologies for monitoring and recording sleep and physiological biomarkers in the natural home environment rather than in a sleep laboratory.

In order to demonstrate the precise physiological effects of OSAS in children and to better understand the mechanisms leading to impairments that are difficult to determine from cross sectional studies, longitudinal and interventional randomized controlled studies are needed. An example of such a study is the childhood adenotonsillectomy (CHAT) study (Redline et al., 2011), evaluating neurocognitive and cardiovascular outcomes in children 5–10 years old, undergoing adenotonsillectomy compared to children in which surgery was delayed and were under close observation.

Another important aspect relates to the genetic susceptibility of individuals to the various OSAS insults like intermittent hypoxia, sleep fragmentation and sleeps loss. Studies using advanced genetic approaches should strive to identify particular genes associated with physiological vulnerabilities. An example of such susceptibility could be demonstrated in regard to apolipoprotein E. This apolipoprotein found in chylomicrons has an important function in

transport and metabolism of lipoproteins. The gene is polymorphic and has three known isoforms. The ApoE4 allele has been strongly associated with atherosclerosis and Alzheimer's disease. Moreover, children and adults carrying ApoE4 were shown to be more susceptible to neurocognitive deficits associated with OSAS compared to those carrying other alleles (Gozal et al., 2007a; Spira et al., 2008). Thus, knowledge about the various genes regulating the physiological impacts of OSAS may help identify groups at risk on one hand and on the other hand understand the mechanisms by which other groups are protected from similar physiological insults.

Finally, there is a need to incorporate advanced methodologies to detect the functional, inflammatory, metabolic, and endocrine impact of OSAS into this line of research. Many of these methods such as MRI spectroscopy and glucose clamp studies are available but not readily used for pediatric research. The use of such approaches will allow new insights into understanding the short and long term impact of OSAS on children.

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