Pathophysiology of Upper Airway Obstruction: a Developmental Perspective
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Abstract: The obstructive sleep apnea syndrome (OSAS) occurs in patients of all ages, from the premature infant to the elderly. Much remains unknown about the pathophysiology of the syndrome. However, research suggests that OSAS in all age groups is due to a combination of both anatomic airway narrowing and abnormal upper airway neuromotor tone. The anatomic predisposing factors for OSAS differ over the lifespan. However, a smaller upper airway is noted in all age groups and probably predisposes to airway collapse during sleep. Despite the known anatomic factors, such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy, that contribute to OSAS throughout life, a clear anatomic factor cannot always be identified. This suggests that alterations in upper airway neuromotor tone also play an important role in the etiology of OSAS.

INTRODUCTION

THE STRUCTURE AND THE NEURAL CONTROL OF THE UPPER AIRWAY HAVE EVOLVED TO SERVE 3 IMPORTANT PHYSIOLOGIC FUNCTIONS: (1) RESPIRATION, (2) DEGLUTITION, AND (3) SPEECH. The upper airway is collapsible in order to accommodate these functions. During wakefulness, upper airway collapse can be prevented by an increase in pharyngeal neuromuscular tone. However, this mechanism is decreased during sleep, predisposing the upper airway to obstruction.

The obstructive sleep apnea syndrome (OSAS) refers to a breathing disorder characterized by recurrent, partial or complete episodes of upper airway obstruction, commonly associated with intermittent hypoxemia and sleep fragmentation. OSAS affects individuals of all ages, from neonates to the elderly. However, it is still not known whether OSAS represents a continuum of a disorder that places pediatric patients at risk for the disease as adults or whether OSAS during different stages of life comprises distinct clinical entities (Table 1). The present review will summarize what is known about the potential anatomic and functional mechanisms leading to OSAS during infancy, childhood, adolescence, and adulthood to determine common mechanisms for the pathophysiology of the disorder throughout development. This review article focuses on development from term infancy to adulthood but excludes the elderly population and does not focus in detail on the premature infant. The review concentrates on the anatomic and neuromotor risk factors for upper airway obstruction. Due to space limitations, other factors, such as genetic susceptibility, and environmental factors, such as passive smoking, will not be discussed.

Pharyngeal Development

The anatomy of the newborn pharynx in humans is similar to that of other primates and mammals. The uvula and epiglottis are in close proximity, creating a secure airway that allows for independent suckling and breathing. This anatomic relationship is maintained in other mammals throughout life, with discrete pathways for respiration and deglutition. However, in the human, at about 18 months of development, the larynx descends to the level of the fifth cervical vertebrae. This anatomic formation develops because of the additional role of the human pharynx of phonation. For the purpose of deglutition, the pharynx functions as a flexible tube, the muscles of which, namely the pharyngeal constrictors and tongue, force food from the oral cavity into the esophagus. For phonation, the pharynx functions as a muscular tube that can change its length and shape to alter the sounds generated by the larynx and passing through the pharynx. For respiration, the pharynx must remain as rigid as possible in order to allow air passage without collapse. However, despite the importance of respiration to sustain life, when one considers the muscles of the upper airway in the human (Table 2), it becomes apparent that not one of these muscles has a primary function of pharyngeal dilation. It is speculated that the lack of such pharyngeal dilators in humans resulted from the absence of an evolutionary need in mammals and primates because the anatomic orientation of the structures securing their upper airway is maintained throughout development, whereas in the human it is not.

Pharyngeal Anatomy

The pharynx is generally divided into 3 anatomic regions (Figure 1). (1) The nasopharynx is located superior to the level of the soft palate and is continuous anteriorly, through the choanae, with the nasal cavities. (2) The oropharynx is located between the
level of the soft palate and the larynx, communicating anteriorly with the oral cavity, and having the posterior one third of the tongue as its anterior border. Based on a midsagittal view, the oropharynx is subdivided into retropalatal (bounded by the level of the hard palate and the caudal margin of the soft palate) and retroglossal (bounded by the caudal margin of the soft palate to the tip of the epiglottis) regions. In infants and young children, the oropharynx includes mostly the retropalatal region, since the soft palate and the epiglottis are in close proximity (Figure 1: A, B). The anterior oropharyngeal wall is formed primarily by the

<table>
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<th>Childhood</th>
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<tr>
<td>Estimated prevalence, %</td>
<td>?</td>
<td>2</td>
<td>2</td>
<td>4-9</td>
</tr>
<tr>
<td>Peak age, y</td>
<td>&lt; 1</td>
<td>2-8</td>
<td>12-18</td>
<td>30-60</td>
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<td>M &gt; F</td>
<td>M = F</td>
<td>?</td>
<td>M &gt; F</td>
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<tr>
<td>Weight</td>
<td>Normal</td>
<td>Normal; May be underweight or obese</td>
<td>Obese</td>
<td>Obese</td>
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<td>Risk factors</td>
<td>Craniofacial anomalies</td>
<td>Adenotonsillar hypertrophy</td>
<td>Obesity</td>
<td>Adenotonsillar hypertrophy</td>
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<td>Obesity</td>
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<td>Gastroesophageal reflux</td>
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<tr>
<td>Adenotonsillar hypertrophy</td>
<td></td>
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<td></td>
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<tr>
<td>Level of obstruction</td>
<td>Nasopharyngeal</td>
<td>Nasopharyngeal</td>
<td>?</td>
<td>Retropalatal</td>
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<tr>
<td>Retropalatal</td>
<td></td>
<td></td>
<td></td>
<td>Retroglossal</td>
</tr>
<tr>
<td>Anatomic findings</td>
<td>Airway</td>
<td>Small?</td>
<td>Small</td>
<td>Small?</td>
</tr>
<tr>
<td>Craniomaxillofacial features</td>
<td>May have craniofacial anomalies</td>
<td>Majority normal</td>
<td>?</td>
<td>Retrognathia</td>
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<tr>
<td>- midfacial hypoplasia</td>
<td></td>
<td></td>
<td></td>
<td>Micrognathia</td>
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<tr>
<td>- micrognathia</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Soft tissues</td>
<td>May have adenoidal hypertrophy; usually normal tonsils</td>
<td>Adenotonsillar hypertrophy</td>
<td>Adenotonsillar hypertrophy</td>
<td>Large lateral pharyngeal walls, tongue, soft palate, parapharyngeal fat pads</td>
</tr>
<tr>
<td>Functional findings</td>
<td>Ventilatory drive</td>
<td>Normal subjects</td>
<td>High?</td>
<td>High</td>
</tr>
<tr>
<td>OSAS</td>
<td>?</td>
<td>Overall normal; some with subtle abnormalities</td>
<td>?</td>
<td>Studies conflicting</td>
</tr>
<tr>
<td>Arousability</td>
<td>Normal subjects</td>
<td>Low</td>
<td>Very low</td>
<td>Moderate</td>
</tr>
<tr>
<td>OSAS</td>
<td>Very low</td>
<td>Very low</td>
<td>?</td>
<td>High</td>
</tr>
<tr>
<td>Upper airway collapsibility</td>
<td>Normal subjects</td>
<td>Very low</td>
<td>Very low</td>
<td>Low</td>
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<tr>
<td>OSAS</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Upper airway reflexes during sleep</td>
<td>Normal subjects</td>
<td>Brisk</td>
<td>Active</td>
<td>?</td>
</tr>
<tr>
<td>OSAS</td>
<td>?</td>
<td>Blunted</td>
<td>?</td>
<td>Low</td>
</tr>
<tr>
<td>Treatment</td>
<td>Treatment of choice</td>
<td>Craniofacial surgery</td>
<td>Adenotonsillectomy</td>
<td>CPAP</td>
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<tr>
<td>CPAP</td>
<td></td>
<td></td>
<td>Weight reduction</td>
<td>CPAP</td>
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<tr>
<td>Adenotonsillectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

M refers to male; F, female; OSAS, obstructive sleep apnea syndrome; CPAP, continuous positive airway pressure
tongue and soft palate, while the posterior wall of the oropharynx is formed by the superior, middle, and inferior constrictor muscles.11,12 The lateral pharyngeal walls are formed by several different soft tissues, including muscles (hyoglossus, styloglossus, stylohyoid, stylopharyngeus, palatoglossus, palatopharyngeus, and the lateral aspects of the superior, middle, and inferior pharyngeal constrictors13, 14); lymphoid tissue, primarily the palatine tonsils (noted more in children) 15; and adipose tissue (lateral parapharyngeal fat pads) (Figure 1: C, D). (3) The hypopharynx is located posterolateral to the larynx and communicates with the cavity of the larynx through the auditus. This includes the pyriform recesses and the valleculae.

**Biomechanical Considerations**

The Starling resistor model, which has been well characterized for a number of biologic systems (such as blood vessels16 and the lower airways17), has been shown to be applicable to the upper airway in OSAS.18,19 This model describes the major determinants of airflow in terms of the mechanical properties of collapsible tubes. The Starling resistor model predicts that, under conditions of flow limitation, maximal inspiratory airflow is determined by the pressure changes upstream (nasal) to a collapsible locus of the upper airway and is independent of the downstream (tracheal) pressure generated by the diaphragm.

The upper airway can be represented as a tube with a collapsible segment, the resistance of which is equal to zero. The segments upstream (ie, nasal) and downstream (ie, hypopharyngeal) from the collapsible segment have fixed diameters and resistances. In this model of the upper airway, inflow pressure at the airway opening (the nares) is atmospheric, and downstream pressure is equal to tracheal pressure (generated by the diaphragm). Collapse occurs when the pressure surrounding the collapsible segment of the upper airway (critical tissue pressure, \( P_{crit} \)) becomes greater than the pressure within the collapsible segment of the airway. In the normal subject with low upstream resistance or markedly subatmospheric \( P_{crit} \), downstream pressure never approaches \( P_{crit} \); thus, airflow is not limited and is largely determined by negative tracheal (inspiratory) pressure. However, if downstream pressure falls below \( P_{crit} \), inspiratory flow reaches a maximum (inspiratory airflow limitation) and becomes independent of downstream pressure swings. Under these circumstances, nasal resistance and \( P_{crit} \) determine maximal inspiratory flow (\( V_{max} \), as described by the following equation: \( V_{max} = (P_N - P_{crit})/R_N \); where \( P_N = \) nasal pressure and \( R_N = \) nasal resistance. Airflow will become zero (ie, the airway will occlude) when \( P_N \) falls below \( P_{crit} \). It is important to realize that in the living human, \( P_{crit} \) reflects both structural and neuromotor factors, as the upper airway is not merely a passive conduit affected by mechanical forces, but is also affected by activation of the upper airway muscles.

**THE ROLE OF ANATOMIC FACTORS IN THE PATHOPHYSIOLOGY OF OSAS**

**Infancy**

OSAS has been described in premature infants, newborns, and infants during the first year of life. Criteria and definitions for OSAS in these groups vary between investigators. The exact prevalence of OSAS early in infancy is not well documented. It is a more frequent phenomenon in premature infants than in full-term infants and continues to decrease with postnatal age until 43 weeks postconceptional age.20 Preterm infants may have OSAS

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**Table 2—Important Upper Airway Muscles and Action**

<table>
<thead>
<tr>
<th>Location</th>
<th>Muscle</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose</td>
<td>Dilator naris</td>
<td>Dilates the ala laterally</td>
</tr>
<tr>
<td></td>
<td>Alae nasi</td>
<td>Elevates the mobile alar cartilage and flares the nostrils</td>
</tr>
<tr>
<td>Lips</td>
<td>Musculus orbicularis oris</td>
<td>Constricts lips</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Tensor veli palatini</td>
<td>Tenses the soft palate</td>
</tr>
<tr>
<td></td>
<td>Levator veli palatini</td>
<td>Elevates the soft palate</td>
</tr>
<tr>
<td></td>
<td>Musculus uvulae</td>
<td>Shortens the uvula</td>
</tr>
<tr>
<td></td>
<td>Palatoglossus</td>
<td>Elevates and retracts the posterior portion of the tongue</td>
</tr>
<tr>
<td></td>
<td>Palatopharyngeus</td>
<td>Elevates the pharynx</td>
</tr>
<tr>
<td></td>
<td>Genioglossus</td>
<td>Protrudes and depresses the tongue</td>
</tr>
<tr>
<td></td>
<td>Hyoglossus</td>
<td>Depresses and retracts the tongue</td>
</tr>
<tr>
<td></td>
<td>Styloglossus</td>
<td>Elevates and retracts the tongue</td>
</tr>
<tr>
<td></td>
<td>Superior, middle constrictors</td>
<td>Constrict the pharynx</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>Digastric</td>
<td>Elevates the hyoid, depresses the mandible</td>
</tr>
<tr>
<td></td>
<td>Stylohyoid</td>
<td>Elevates the hyoid</td>
</tr>
<tr>
<td></td>
<td>Mylohyoid</td>
<td>Elevates the hyoid and tongue; depresses mandible</td>
</tr>
<tr>
<td></td>
<td>Geniohyoid</td>
<td>Elevates and displaces the hyoid forward; depresses the mandible</td>
</tr>
<tr>
<td></td>
<td>Omohyoid</td>
<td>Depresses the hyoid</td>
</tr>
<tr>
<td></td>
<td>Sternohyoid</td>
<td>Depresses the hyoid</td>
</tr>
<tr>
<td></td>
<td>Thyrohyoid</td>
<td>Depresses the hyoid</td>
</tr>
<tr>
<td></td>
<td>Sternothyroid</td>
<td>Depresses the hyoid</td>
</tr>
<tr>
<td></td>
<td>Inferior constrictor</td>
<td>Constricts the pharynx</td>
</tr>
<tr>
<td>Larynx</td>
<td>Posterior cricoarytenoid</td>
<td>Abducts and laterally rotates arytenoid cartilage</td>
</tr>
</tbody>
</table>

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secondary to hypotonia and central nervous system immaturity. Neonates with craniofacial anomalies often have OSAS. In some young infants, OSAS may be idiopathic. After the first few months of life, adenoidal hypertrophy, and subsequently tonsillar hypertrophy, may develop and contribute to OSAS.

Premature and newborn infants are predisposed to upper airway obstruction and oxygen desaturation during sleep mainly because of decreased upper airway muscle tone, high nasal resistance, and a highly compliant chest wall. Dransfield et al. found that 68% of them had obstructive events, whereas 32% had only central events. Milner et al. found that half of the apneic events associated with periodic breathing in 8 premature infants were the result of upper airway obstruction and glottic closure. Spontaneous neck flexion was also found to cause upper airway obstruction in premature infants.

Studies on full-term infants show that obstructive events occur mostly during active sleep, are more frequently observed in males, and usually resolve by 8 weeks of life. In full-term infants, Kahn et al. found a median obstructive apnea index of

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**Figure 1**—A midsagittal magnetic resonance image (MRI) of the head of a child (A) and an adult (B) are shown. The airway is shown in black. Note the 3 main anatomic regions of the upper airway in the child: nasopharynx (NP), oropharynx adjacent to the retropalatal region (OP<sub>RP</sub>), and hypopharynx (HP). The adult airway differs from that of the child by having, in addition, an oropharyngeal segment that is retroglossal (OP<sub>RG</sub>). 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. An axial MRI of the head at the retropalatal level of a child (C) and an adult (D) are shown. The airway is shown in black. The lateral pharyngeal walls (PW) in the child are formed mainly by the palatine tonsils (T). In the adult, the tonsils are usually absent or minimal in size and the PW is formed by a combination of muscles (see text for details).
OSAS is not likely to be attributable to adenotonsillar hypertrophy. Full-term neonates are preferential nasal breathers and may develop upper airway obstruction whenever mild nasal obstruction, such as an upper respiratory infection, is present. In addition, a highly compliant chest wall predisposes newborn infants to gas-exchange abnormalities during even brief episodes of obstruction. Don et al. studied the anatomic site of upper airway obstruction in 19 infants between 1 and 36 weeks of age evaluated for possible OSAS. They used a combination of magnetic resonance imaging (MRI) and airway manometry to evaluate the site of obstruction. Obstruction with clinically significant OSAS (respiratory disturbance index > 3 per hour) occurred in the retropalatal region 80% of the time, and in the retroglossal region, 20% of the time.

Infants may present with upper airway obstruction and at times apparent life-threatening events (ALTEs) when severe gastroesophageal reflux is present. Upper airway obstruction may be due to edema of the upper airway, laryngospasm, or aspiration of gastric contents. In addition, these infants can have central apnea as a vagal reflex response. In infants over 6 months of age, the association of snoring, obstructive apnea, failure to thrive, developmental delay, and adenotonsillar hypertrophy has been established by several investigators. These studies have also demonstrated the efficacy of early adenotonsillectomy in decreasing the morbidity of OSAS in this young age group.

Several reports have described the association between OSAS and ALTE during early infancy. Guillemainault et al reported a high number of mixed and obstructive apnic events in infants with ALTEs. Moreover, a report from the same group described 5 infants with ALTEs who subsequently developed severe OSAS. Polysomnography in these infants at the time of the initial ALTE (3 weeks to 6 months of age) demonstrated a high index of mixed and obstructive events. These infants became progressively more symptomatic by 6 to 10 months of age and improved only after adenotonsillectomy, supporting the role of adenotonsillar hypertrophy as a main cause for OSAS in these infants. An association has also been described between obstructive apnea and sudden infant death syndrome (SIDS). Polysomnography was performed in a few infants who subsequently died of SIDS. When compared to age-matched controls, the SIDS infants had a higher number of mixed and obstructive events and a lower number of sighs. These findings suggest that, in addition to an obstructive component, these infants may have a coexisting abnormality in peripheral chemoreceptor function contributing to their death.

A familial association has been described between adults with OSAS and infants who died of SIDS or had ALTEs. Mathur and Douglas found that SIDS occurred more commonly in families with a history of OSAS. Tishler et al. found a significant association between altered cephalometrics, atopy, and decreased hypoxic chemosensitivity in family members with OSAS who had a first-degree relative who died of SIDS or had an ALTE. These findings suggest that genetically determined mechanisms might influence airway size or other mechanisms that could link SIDS, ALTE, and OSAS.

### Risk Factors

Three known risk factors contribute to OSAS in infants: (1) craniofacial anomalies, (2) altered soft tissue size, and (3) neurologic disorders (Table 3).

### Craniofacial Anomalies

The relationship between craniofacial structure and OSAS is most compelling in infants with distinct craniofacial anomalies seen with craniofacial synostosis, such as Crouzon, Pfeiffer, and Apert syndromes, and with mandibulofacial dysostoses, such as Robin sequence and Treacher-Collins syndrome. Altered facial skeletal development, especially the association of maxillary and/or mandibular hypoplasia, may lead to airway narrowing due to crowding of adenoid, tonsils, and other soft tissues within the mid and lower face skeletal boundaries. Decreased neuromotor function, decreased upper airway muscle tone, and decreased upper airway muscle mass may also contribute to these findings.
tor tone may further reduce airway size by inducing glossoptosis and hypopharyngeal collapse during sleep. Children with craniofacial anomalies may present with OSAS soon after birth and during the first years of life. In some cases, OSAS does not occur until the child is older and develops adenotonsillar hypertrophy in conjunction with the narrow upper airway. Some craniofacial syndromes, such as Down syndrome, are also associated with hypotonia, which can contribute to upper airway obstruction. Children with associated central nervous system abnormalities may also have central hypoventilation.

Down syndrome is the most common genetic disorder associated with craniofacial anomalies. OSAS is present in 30% to 60% of these patients. Anatomic factors related to the Down syndrome phenotype, including midfacial and mandibular hypoplasia, glossoptosis, adenoid and tonsillar hypertrophy, laryngotracheal anomalies, and obesity, are the most common causes for OSAS in this group. In addition, reduction in neuromuscular tone may also play a role in the development of sleep-disordered breathing in these children.

Altered Soft Tissue Size

The size of the soft tissues of the upper airway (tonsils, adenoid, fat pads, and musculature) are determined by genetic factors. In addition, the size of these tissues may be affected by inflammation, infection, and infiltration by various metabolic or storage components. Finally, abnormal neuromotor tone may further alter the shape of upper airway musculature, predisposing to airway narrowing and collapse during sleep.

Inflammatory changes leading to adenotonsillar hypertrophy are seen in some infants prior to 1 year of age, leading to the full clinical spectrum of OSAS. Macroglossia can significantly reduce upper airway size. It commonly occurs in infants and children with Down syndrome, as well as in infants and children with various storage and metabolic disorders, such as mucopolysaccharidosis and Beckwith-Wiedemann syndrome. In patients with glossoptosis, the tongue may prolapse posteriorly and occlude the airway. Glossoptosis is commonly seen in patients with a small and retroposed mandible as in the Robin sequence or in conditions associated with poor upper airway muscle tone such as Down syndrome. Anomalies of the soft palate, such as cleft palate and velopharyngeal insufficiency, are not usually associated with OSAS. However, the surgical correction of these malformations by palatoplasty and pharyngeal flap, respectively, are associated at times with a moderate degree of OSAS.

Neurologic Disorders

Various central nervous system disorders have been associated with OSAS in young infants. All induce pharyngeal hypotonia and predispose to sleep-disordered breathing and airway obstruction. Common causes include cerebral palsy, increased intracranial pressure, brain stem compression/dysplasia such as Arnold Chiari malformations, recurrent laryngeal nerve palsy, palsies of the cranial nerves, and syrinx.

Childhood

In preschool-aged children, the incidence of OSAS is estimated to be 2%, whereas primary snoring is more common and is estimated to be 6% to 9% in school-aged children. Although the exact mechanism for OSAS in children is not fully understood, important anatomic risk factors have been identified and are linked to the anatomic structures surrounding the airway that affect the size and shape of the airway. Various techniques such as lateral neck radiographs, cephalometrics, acoustic reflection and MRI have shown that the upper airway of children with OSAS is smaller on average than that of the normal child.

Location of Upper Airway Narrowing

In order to determine the anatomic region of maximal narrowing in children with OSAS, Isono et al performed upper airway endoscopy under general anesthesia, evaluating discrete levels of the upper airway including the adenoid, soft palate, tonsil, and tongue. The minimum cross-sectional area was found to be at the level of the adenoid and the soft palate. These findings, along with high closing pressures noted at these points in the same study, suggest that the superior upper airway segments are most involved in children with OSAS. These findings are supported by recent studies evaluating upper airway size with MRI. Arens et al showed that airway narrowing in children with OSAS occurred along the upper two thirds of the airway (Figures 2 A, C) and was maximal in the region where the adenoid overlapped the tonsils (Figure 3). Similar findings were noted by Fregosi et al, who described maximal narrowing in the retropalatal region where the soft palate, adenoid, and tonsils overlap.

Craniofacial Structure

Several studies using cephalometrics support the idea that children without distinct craniofacial anomalies have subtle craniofacial morphometric features associated with OSAS. Kawashima et al reported that children with OSAS and more pronounced tonsillar hypertrophy have retrogadic mandibles and increased posterior facial height compared to children with OSAS and less pronounced tonsillar hypertrophy. Shintani et al noted that the relationship of the mandible with respect to the cranial base was retrogadic in children with OSAS compared to normal children without OSAS. Zuconi et al noted that children with OSAS had increased craniomandibular, intermaxillary, goniac, and mandibular plane angles, indicating a hyperdivergent growth pattern.

In contrast to the above, other investigators suggest that the craniofacial changes found in children with OSAS are mild and are reversible following adenotonsillectomy. In a recent study evaluating upper airway structure, Arens et al noted no significant differences in the size of the mandible and maxilla of children with OSAS versus controls. Furthermore, in a more comprehensive evaluation of the mandible after 3-dimensional reconstruction, these authors found no difference in 8 dimensions of the mandible between children with OSAS and controls, suggesting that mandibular size and shape does not play a significant role in the causation of childhood OSAS in nonsyndromic children.

Soft Tissues

Adenoid and Tonsils

Soft tissues, particularly the tonsils and adenoid, can also narrow the pharynx. These tissues grow progressively during child-
hood and are maximal in the prepubertal years, coinciding with the peak incidence of childhood OSAS. In normal children, the airway size grows proportionately with the soft tissues surrounding it. However, it is not known how the airway grows in proportion to the surrounding tissues in children with OSAS. In most cases, large tonsils, adenoids, or both could explain the clinical symptoms of children with OSAS, and surgical removal of these tissues cures or ameliorates the disorder in the majority of cases. However, it is estimated that in 10% to 15% of otherwise normal children with OSAS, this disorder is not resolved by the simple removal of the tonsils and adenoids.84-86

Although the importance of adenoidal and tonsillar hypertrophy in the pathogenesis of childhood OSAS is unquestioned, much remains to be learned as only a weak relationship was found between the severity of OSAS and the size of these tissues, when assessed clinically or by simple radiographic methods.87-89

Figure 2—A midsagittal magnetic resonance image (MRI) of the head of a child with obstructive sleep apnea syndrome (OSAS) (A) and an adult with OSAS (B). The airway is shown in black. Note that, in the child, airway narrowing occurs in the nasopharyngeal and high oropharyngeal regions where the adenoid (Ad) and tonsils (T) overlap the airway (arrow). In the adult, airway narrowing is maximal at the low retropalatal and retroglossal regions (arrow). Ad refers to adenoid; SP, soft palate. An axial MRI of the head at the retropalatal level of a child with OSAS (C) and an adult with OSAS (D) are shown. The airway is shown in black. Note tonsillar (T) hypertrophy in the child, narrowing the airway (white arrow). Note that, in the adult, pharyngeal narrowing is such that the anterior-posterior axis is longer than the lateral-lateral axis (arrow).
This weak relationship suggests that the role of the adenoid and tonsils in the pathogenesis of OSAS is more complex than simply being related to their size. It is possible that the 3-dimensional orientation of these tissues, and how they overlap in the airway, is a more important factor and may significantly affect flow resistance during sleep. This is suggested by recent reports using 3-dimensional MRI techniques, showing that maximal airway narrowing occurred in OSAS subjects along an airway segment where both the adenoid and tonsils overlapped (Figure 3). 

**Tongue Size**

The tongue is one of the largest structures defining the oropharyngeal airway and bounds its anterior aspect. It is composed of extrinsic muscles (genioglossus, hyoglossus, and styloglossus), which alter its position, and intrinsic muscles, which alter its shape, both of which can affect airway size and shape. Arens et al. found that the overall volume of the tongue in normal children with OSAS did not differ from controls.

**Soft Palate**

There are few data on the dimensions of the soft palate in children with OSAS. Using direct measurements, Brodsky et al. did not find a correlation between soft-palate length and severity of tonsillar hypertrophy in children with OSAS. Using MRI, Arens et al. noted a 30% increase in the volume of the soft palate of children with OSAS compared to controls. They speculated that the larger palatal volume might have been due to edema and inflammatory changes secondary to chronic snoring, as described in adults.

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**Childhood Obesity**

In adults, obesity is a major risk factor for OSAS. Earlier descriptions of childhood OSAS rarely described obese patients. In fact, many were of normal weight, and failure to thrive was a common complication. However, in the last 20 years, obesity has become the most prevalent nutritional disease of childhood in the United States, affecting almost 1 in 5 children. The current pediatric literature suggests that obesity increases the risk for OSAS in all ages, from early infancy to late childhood. Moreover, in a large epidemiologic study involving 399 children between 2 and 18 years of age, obesity was found to be the most significant risk factor for OSAS, with an odds ratio of 4.5.

In an older study, Guilleminault et al. reported that 10% of children diagnosed with OSAS were obese. This prevalence was similar to the finding reported by Brouillette et al., who also included infants in their study. A higher incidence of OSAS was reported when only obese children were evaluated for OSAS. Silvestri et al. noted OSAS in 59% of symptomatic obese children. Marcus et al. studied obese children and adolescents (aged 10 ± 5 years, 184% ± 36% ideal body weight) who did not present with symptoms of OSAS and found that 46% had abnormal polysomnography and 27% had moderate to severe abnormalities. Moreover, there was a positive correlation between obesity and the apnea index (r = 0.47, P < .05) and an inverse relationship between obesity and oxygen saturation nadir (r = -0.5, P < .01).

Adenotonsillar hypertrophy is not always the main cause for OSAS in obese children, although several authors do emphasize this as an important factor. Obese children may have excess deposition of adipose tissue within the muscles and tissues surrounding the airway, limiting airway size and increasing airway resistance. Other causes include altered chest wall mechanics and reduced lung volumes resulting in decreased oxygen reserves and increasing the likelihood of hypoxemia and a decreased central ventilatory drive.

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**Adolescence**

There are few data related to the epidemiology of OSAS in adolescence. Only one study assessed the prevalence of the disorder in this age group and estimated it at 1.9%. It is not known whether OSAS appearing in adolescence is an extension of the clinical disorder of childhood, with adenotonsillar hypertrophy as a major risk factor, or whether it represents an early manifestation of the adult form of OSAS, with obesity as a major risk factor.

Several studies have addressed the relationship between childhood OSAS and OSAS during adolescence. In a retrospective study, Morton et al. found that sleep-disordered breathing in adolescence was more common in those who had undergone adenotonsillectomy during early childhood. Tasker et al. noted a significant increase in inspiratory effort and snoring during sleep in adolescents 12 years after adenotonsillectomy, compared to controls. The latter authors speculated that airflow narrowing could have originated in childhood and predisposed to OSAS during adolescence. Guilleminault and colleagues noted alterations in craniofacial morphology in 3 adolescents with OSAS and a history of upper airway obstruction in childhood. They hypothesized that both genetic factors altering craniofacial
growth and secondary modification of craniofacial growth secondary to adenotonsillar hypertrophy predisposed these patients to OSAS.110,111

Another possibility is that OSAS during adolescence represents an early manifestation of the adult form of OSAS, especially when associated with obesity. It is well established that the antecedents of adult obesity begin during childhood and adolescence.95 Childhood obesity in all age groups is currently on the rise, and the highest prevalence (15.5%) is seen in adolescent children between 12 and 19 years of age.112 Recent studies have revealed the presence of all components of the metabolic syndrome in this age group.113-115 Finally, a 5-fold rise in the prevalence of OSAS in obese children admitted for hospital care has been observed in recent years.96 The above observation supports an association between the increased prevalence of obesity seen in recent years in children and adolescence and the consequences of the disorder, including OSAS.

Adulthood

The prevalence of OSAS in adults is 4% to 9% and correlates with age, degree of obesity, and male sex.116,117 Most studies suggest that adults with OSAS have a smaller upper airway than do non-OSAS subjects.14,118-125 Pharyngeal narrowing is such that the anterior-posterior axis is longer than the lateral axis. Narrowing is most significant in the retropalatal region (Figure 2, B, D)14,124 and is noted in both the wake and sleep conditions. A smaller airway may be caused by increased size of the soft tissues lateral to the airway or by normally sized soft tissues within a more restricted craniofacial structure.

Craniofacial Structure

Cephalometric, computed tomography, and MRI studies have demonstrated craniofacial abnormalities in adults with sleep apnea, including a reduction in mandibular body length, retrognathia, reduced mandibular enclosure area, retroposition of the maxilla and an inferiorly positioned hyoid bone.123,126-135 However, of all craniofacial measurements, it seems that only mandibular body length has clinical significance for predicting OSAS.136 Studies using cephalometrics suggest that alterations in craniofacial structure have a genetic component.137,138 Using cephalometrics, Guilleminault et al138 showed that first-degree family members of patients with OSAS had less maxillary protrusion (SNB), an inferior position of the mandible (longer MPH), and a decreased posterior airway space. Mathur and Douglas139 used a combination of airway-imaging modalities to show that both cephalometric and acoustic reflection measurements were altered in first-degree relative of patients with OSAS. These findings of genetic susceptibility are supported by large epidemiologic studies showing that OSAS is more prevalent in the relatives of index probands (21%) than among neighborhood control subjects (12%; P = .02).140 Other studies have shown craniofacial differences between different ethnic groups,137,141,142 and the 2 sexes.143 Thus, the above studies support the notion that genetic factors affecting craniofacial morphology could be one factor in the aggregation of OSAS in families, predisposition in certain ethnicities, and the predisposition to OSAS in men compared to women. However, other reasons for a familial predisposition to OSAS include the heredity of the ventilatory drive144 and the familial occurrence of obesity.

Soft Tissues

In addition to changes in craniofacial structure, soft tissue structures of the upper airway have been shown to be larger in adults with OSAS. On average, adults with OSAS have been shown to have an increased size of the soft palate, tongue, parapharyngeal fat pads, and lateral pharyngeal walls.14,119,145-149 No single tissue has been identified as the primary cause of upper airway narrowing.14,149,150 It is likely that all the tissues mentioned above interact to narrow the upper airway lumen, which predisposes the airway to closure during sleep. Possible mechanisms to explain the increase in size of these soft tissue include (1) obesity, (2) edema and inflammation, (3) a primary muscle disorder, (4) genetic factors, and (5) factors related to sex.

Obesity

Obesity is an important risk factor for OSAS in adults.116,151 An increase in neck circumference has been found to be the most important clinical predictor for OSAS in this age group.116,152 About one half of American adults are considered to be overweight (BMI > 25 kg/m2), and nearly a quarter are obese (BMI > 30 kg/m2).153 In the Wisconsin Sleep Cohort Study,116 an increase in BMI of 1 SD tripled the prevalence of OSAS.

The importance of a large neck circumference in adults with OSAS is supported by many studies showing increased deposition of fat around the upper airway in both obese and nonobese subjects with OSAS. Fat deposition is mostly noted in the parapharyngeal fat pad region.14,105,154-157 However, increased fat deposition has also been noted in the tongue and soft palate.158,159 The mechanism by which increased fat in these tissues leads to OSAS is still unclear. Shelton and colleagues159 suggested that fat deposited in the space bounded by the mandibular rami leads to increased tissue pressure, which, in turn, can result in airway narrowing and collapse during sleep.

In addition to increased adipose tissue, weight gain also increases muscle mass.160 This suggests that obesity may predispose individuals to sleep apnea by directly increasing the size of the upper airway soft tissue structures, in addition to the fat that is deposited in these tissues.157 Finally, obesity may have indirect effects by altering upper airway compliance and changing the biomechanical relationships of the upper airway muscles.151

Edema

Although increased soft tissue size surrounding the airway as a cause for OSAS is primarily related to obesity, chronic edema and inflammation of the upper airway soft tissues may further restrict the dimensions of the upper airway. The mechanism for this effect is speculated to be the effect of chronic vibratory effects of snoring and of upper airway soft tissue being tugged caudally during fluctuation in intrathoracic pressure, resulting in trauma to the upper airway soft tissues.92,93 Indeed, the therapeutic effect of CPAP is thought to be partially mediated through a reduction in upper airway soft tissue edema, and the use of CPAP has been shown to reduce soft palate volume.148

Myopathy

It has been suggested that patients with OSAS have a primary myopathy. Several studies have demonstrated an increase in type II fast-twitch fibers in the genioglossus of patients with
OSAS. Type II fibers are less resistant to fatigue than type I fibers. It is possible that the increased number of type II fibers is secondary to chronic muscle injury, which, in turn, may alter the size, length, and configuration of the affected muscles.

Genetic factors

The influence of genetic factors on the size of upper airway soft tissue structures has not been carefully studied. Nonetheless, the size and shape of the tongue, soft palate, and lateral pharyngeal walls may all be genetically determined. Studies are needed to determine whether enlargement of the upper airway soft tissue structures in patients with sleep apnea demonstrates familial aggregation and heredibility. Such studies could be performed with MRI since it can accurately quantify upper airway soft tissue volumes and craniofacial structure.

Sex

In adults, OSAS is far more common in men than women. Considerable effort has been expended in trying to determine the mechanisms underlying this male predominance, but no clear explanation has emerged. Studies have not shown differences in pharyngeal anatomy resulting in a smaller pharyngeal lumen in men. On the contrary, women have been found to have a narrower and shorter pharynx, despite the presence of larger soft tissues in men. It is therefore possible that the reduced occurrence of OSAS in women is due to a stiffer and less collapsible upper airway despite its smaller size. Speculated mechanisms mediating differences in airway collapsibility include hormonal differences, differences in chemosensitivity, and differences in tissue properties.

Summary of Anatomic Factors

Various anatomic and functional mechanisms may lead to OSAS in children and in adults. However, a smaller upper airway is noted in all age groups and probably predisposes to airway narrowing and collapse during sleep. OSAS is uncommon in infancy. However, children born with craniofacial anomalies are at increased risk for the development of a severe form of the disorder.

The most common type of childhood OSAS occurs in children between 2 and 8 years of age and is associated with adenotonsillar hypertrophy in most cases. Surgical removal of the adenoid and tonsils ameliorates the disorder in most but not all children, suggesting that other mechanisms such as those leading to altered upper airway neuromotor tone during sleep may contribute to OSAS in these children.

Recent data suggest that obesity may be a leading cause for OSAS during adolescent years. This form of OSAS shares much with the adult form of OSAS. Additional factors that may cause restriction of the upper airway in adolescents include adenotonsillar hypertrophy and altered craniofacial morphology.

The adult form of OSAS commonly occurs in middle age. It is strongly associated with obesity, male sex, and familial aggregation. Mild alterations in craniofacial morphology and soft tissues size surrounding the upper airway are commonly noted.

In summary, there are known anatomic factors such as craniofacial anomalies, obesity, and adenotonsillar hypertrophy that contribute to OSAS throughout life. However, it should be emphasized that a clear anatomic factor cannot always be identified, suggesting that subtle changes in craniofacial structure morphology, alterations in upper airway neuromotor tone, or both may also play a role in the causation of OSAS.

THE ROLE OF NEUROMOTOR FACTORS IN THE PATHOPHYSIOLOGY OF OSAS

The preceding evidence has shown that structural factors play an important role in the pathogenesis of OSAS. However, neuromotor factors also play a critical role in the development of upper airway collapse. This is evidenced by the fact that obstructive apnea only occurs during sleep, when upper airway muscle tone is diminished, even though the same structural factors are present during both wakefulness and sleep. Furthermore, although many studies have shown that patients with OSAS have narrower airways than normal subjects, there is usually substantial overlap between the groups, and anatomic factors (such as adenotonsillar hypertrophy in children) can explain only part of the predilection for airway collapse. These facts suggest that patients with OSAS are predisposed to OSAS due to a narrower airway but that neuromotor factors also play a role. Such neuromotor factors may include abnormalities of the central nervous system ventilatory drive, as well as local upper airway muscle tone, upper airway sensation, and upper airway reflexes.

Upper airway muscle tone decreases with sleep onset. A question remains as to whether patients with OSAS have a relatively greater decrement in upper airway tone on sleep onset compared to normals, and therefore develop obstructive apnea, or whether they have a “normal” decrement in tone on sleep onset but an increased structural load, and therefore obstruct.

The following sections describe what is known about the role of the central ventilatory drive and upper airway neuromotor tone in the pathophysiology of OSAS across the age spectrum. Unless specifically mentioned, data on adolescents are unavailable.

Central Ventilatory Drive

The ventilatory drive changes with age. Few studies have directly compared different age groups, and differences in technique make it difficult to compare the results of different studies, particularly those comparing infants to older age groups. Typically, studies in infants have been conducted with the infant asleep and breathing through a mask, whereas studies in older children and adults have evaluated awake subjects breathing through a mouthpiece. Furthermore, in studies evaluating rebreathing responses, the difference in body size and hence tidal volume needs to be taken into account. The occlusion pressure in 100 milliseconds (P0.1) may be a better measurement of ventilatory drive than rebreathing responses, as it is not affected by body size and is less affected by changes in thoracic or upper airway mechanics. However, even studies evaluating P0.1 between the age groups can be criticized, as P0.1 can be affected by differences in mechanical factors in addition to differences in ventilatory control.

The airway occlusion pressure is generated primarily by the diaphragm, which is the major inspiratory muscle. Changes in the configuration of the diaphragm will affect the force generated by the diaphragm. The configuration of the ribs and the angle of insertion of the diaphragm changes with age. The configuration of the diaphragm is also affected by the...
resting lung volume, which is smaller in children than in adults. In addition, children have a more compliant rib cage than adults, rendering the thorax more susceptible to distortion during the P_{0.1} maneuver.\textsuperscript{173} Further, children have a longer time constant than adults, which can result in a phase shift between pressure and flow measurements.\textsuperscript{172} Thus, the following studies comparing the ventilatory drive between infants and older subjects need to be interpreted with caution.

**Ventilatory Drive During Wakefulness**

In one of the few studies spanning the age range, Avery et al.\textsuperscript{174} showed no difference in the slope of the hypercapnic ventilatory response, corrected for body weight, between 8 neonates and 10 adults. However, the younger subjects had a left shift of the hypercapnic curve (ie, a lower CO\textsubscript{2} threshold). Gaultier et al.\textsuperscript{175} compared resting ventilatory parameters and the P_{0.1} between children (aged 4-16 years) and adults (aged 18-32 years). The authors found that P_{0.1} decreased with age, reaching adult levels at approximately 13 years of age. Cosgrove et al.\textsuperscript{176} evaluated the ventilatory and P_{0.1} responses to hypercapnia in neonates versus older subjects ranging from 6 to 50 years of age. This publication does not clearly describe the methods used for the neonates. It appears that neonates were studied with a mask and older subjects with a mouthpiece, but it is not clear whether the neonates were studied awake or asleep. The investigators found that the hypercapnic response increased with age. However, correcting the raw data of their hypercapnic ventilatory responses for weight showed that the slope of the adjusted hypercapnic ventilatory response declined with age (r = -0.34, P < .01). In contrast, P_{0.1} did not vary significantly with age. Marcus et al.\textsuperscript{177} studied hypercapnic and hypoxic ventilatory responses in 59 subjects ranging in age from 4 to 49 years. They found significant correlations between both the awake hypercapnic (r = -0.57, P < .001) and hypoxic (r = 0.34, P < .05) ventilatory responses, corrected for body size and age. Thus, when corrected for size, young children had a high ventilatory drive. This decreased during adolescence and stabilized during adulthood (Figure 4). Similarly, studies during exercise have shown that the peripheral chemoreceptor response is greater in school-aged children than in adults.\textsuperscript{178} Kawakami et al.\textsuperscript{179} found that the hypoxic ventilatory response was higher in adolescent males than adult males, although the hypercapnic ventilatory response was similar. Hirshman et al.\textsuperscript{180} and Patrick et al.\textsuperscript{181} showed no correlation between age and ventilatory responses in young adults, ranging from 20 to 44 years of age. However, Kronenberg et al.\textsuperscript{182} showed that ventilatory responses were higher in younger adults (22-30 years old) than older adults (64-73 years old). In a longitudinal study, Nishimura et al.\textsuperscript{183} showed a decline in the hypoxic ventilatory response, but not the hypercapnic ventilatory response, with aging in young adults.

In summary, the evaluation of the development of ventilatory drive is controversial, as it is unclear how best to correct for differences in body size. It is basically impossible to compare studies in infants to those of older subjects, due to the need to study infants with masks and during sleep. However, the preponderance of evidence suggests that there is a continuum in ventilatory responses, which decline from childhood through adolescence, adulthood, and old age. The reason for the elevated ventilatory responses found in children is not known but may be related to their high basal metabolic rate, which is 1 of the factors determining ventilatory drive.

**Ventilatory Drive During Sleep**

Classically, the central ventilatory response to hypoxia and hypercapnia has been thought to be lower during sleep than wakefulness.\textsuperscript{184} Newer studies suggest that this is not true. Although there is less ventilation in response to a hypoxic or hypercapnic stimulus during sleep, this may be related to the mechanical changes that occur during sleep, such as the increase in upper airway resistance,\textsuperscript{185} rather than on a central basis.

**Ventilatory Drive in OSAS**

The role of the ventilatory drive in patients with OSAS remains unclear. Modeling studies suggest that patients with OSAS have a high gain ventilatory control system, resulting in ventilatory instability and hence apnea.\textsuperscript{186,187} Clinically, most studies have evaluated rebreathing hypoxic or hypercapnic responses in adults and were performed only during wakefulness. These studies have shown conflicting results. Some studies found a blunted drive (often improving after treatment), others found a normal drive, and others found abnormalities only in subsets of patients.\textsuperscript{144,188-189} These studies all involved confounding factors, including obesity, chronic obstructive pulmonary disease, and awake hypoventilation. In contrast, studies in children have shown normal overall ventilatory responses to hypoxia and hypercapnia during both wakefulness\textsuperscript{190} and sleep.\textsuperscript{191} The differences in children compared to adults may be due to the decreased number of confounding factors in the children (in the pediatric studies, 10%-40% of the OSAS children were obese, compared to 0%-10% of controls), to the fact that OSAS in children is likely to have been milder and of shorter duration than in the adults, or to a true difference in pathophysiology between the age groups. Although the overall rebreathing ventilatory responses are normal in children with OSAS, subtle abnormalities may exist. Gozal et al.\textsuperscript{192} performed repetitive hypercapnic challenges during wakefulness...
early in the morning in children with OSAS who were hypercapnic during sleep. The children with OSAS mounted a respiratory response to the CO₂ challenge but did not show the same adaptive changes in respiratory pattern over the course of multiple challenges as the normal children did. When studied later in the day or after treatment of OSAS, the OSAS group had a similar respiratory pattern to the controls, suggesting that these deficits were due to habituation to nocturnal hypercapnia or other sleep- or circadian-related factors. This is supported by data from children with OSAS showing an inverse correlation between the duration of hypercapnia during polysomnography and the awake hypercapnic ventilatory response.197

In one small study, P₀.₁ was measured in 17 children and adults during wakefulness, and 8 of these subjects during sleep.200 The results were compared to the slope of the pressure-flow curve during sleep, a marker of upper airway collapsibility (see section on upper airway neuromotor tone, below). No correlation was found between the P₀.₁ during wakefulness and the slope of the pressure-flow curve (r = 0.28, NS). However, there was a strong inverse correlation between P₀.₁ asleep and slope (r = -0.80, P < .02). This suggests that the central ventilatory drive affects upper airway collapsibility. The fact that the slope of the pressure-flow curve correlated with P₀.₁ during sleep but not during wakefulness demonstrates that deficits in ventilatory drive may be sleep-state specific.

Few studies have evaluated the ventilatory drive specifically in infants with OSAS, although there are many studies evaluating infants with ALTEs. In general, infants have a strong biphasic response to hypoxemia, with an initial increase in ventilation, followed by a sustained depression of ventilation. This ventilatory roll off is much more pronounced than in adults.201 Theoretically, this can lead to ventilatory instability and may be one of the reasons for the high prevalence of apnea (both central and obstructive) in the preterm infant.

**Ventilatory Response to Inspiratory Loading**

**Normal Subjects**

Sleep onset is associated with a marked increase in upper airway resistance.185 This is one of the reasons for the relative hypoventilation that occurs during sleep compared to wakefulness. In order to understand the effects of this increase in resistance, studies have evaluated the response to exogenous inspiratory loads during wakefulness and sleep. During wakefulness in normal adults, there is an immediate perception of the load, coupled with an immediate ventilatory compensatory response. This is thought to be cortically mediated. As a result, there is a prolonged inspiratory time (resulting in an increased Tᵢ/TTOT ratio) and maintenance of normal ventilation. During sleep, there is a prompt ventilatory response to total airway occlusion, frequently associated with arousal.202 However, there is no immediate response to an increased inspiratory load short of total occlusion. Instead, there is a decrease in minute ventilation, resulting in hypoventilation. This is followed by a delayed compensatory response that is thought to develop secondary to gas exchange abnormalities, rather than to the load itself.202

Few data exist regarding the response to inspiratory resistive loading in normal children. Adolescents appear to have normal sensation in response to upper airway occlusion during wakefulness; data on younger children are not available. During sleep, normal children increase their Tᵢ/TTOT ratio in response to inspiratory loading, but even with this compensatory response, they have a marked decrease in minute ventilation. In one study, the minute ventilation dropped by as much as 40% in response to an inspiratory resistive load of 15 cm H₂O/L per minute.205 Unlike adults, the minute ventilation failed to improve substantially over time (for at least 3 minutes).

Most studies of inspiratory loading in infants have focused on the premature infant. All infant studies have been conducted during sleep. Although preterm infants show a brisk genioglossal electromyogram (EMG) response to upper airway occlusion or increased resistance206,207 and have an increase in the Tᵢ/TTOT ratio,206-209 they have an immediate and sustained decline in minute ventilation.208 Full-term infants have also been shown to have a decrease in minute ventilation in response to increased upper airway resistance.210

Thus, all age groups fail to compensate immediately in response to inspiratory resistive loading during sleep, but normal adults tend to have a late (3-4 minutes) compensatory response, whereas normal infants and children do not.

**Subjects with OSAS**

A number of studies suggest that patients with OSAS, both adult and pediatric, have abnormal responses to inspiratory resistive loading. Studies comparing adult OSAS patients with weight-matched controls have shown that adults with OSAS have a decreased perception of inspiratory resistive loads during wakefulness.211,212 During wakefulness, adults with OSAS have decreased compensatory responses for inspiratory resistive loading, as compared to weight-matched controls.213,214 Both the load perception and the ventilatory response to loading improve following continuous positive airway pressure therapy, suggesting that the impaired response to inspiratory resistive loading is a consequence rather than a cause of OSAS.212,214 In the only study of children, it was found that children with OSAS aroused at a significantly higher inspiratory resistive load than did controls.205 The arousal threshold was particularly high during REM sleep, which is when most pediatric OSAS occurs.215 This lack of arousal in children with OSAS, and presumed lack of a ventilatory compensation to loading (as in normal children), may contribute to the presence of prolonged obstructive hypoventilation (prolonged periods of partial upper airway obstruction associated with hypercapnia, Figure 5).

In preterm infants with either central or obstructive apnea, imposed upper airway occlusion results in a prolongation of inspiratory time similar to that seen in controls but a reduced genioglossal EMG response.206 The imposition of exogenous upper airway occlusion frequently results in either central or obstructive apneas.216

**Arousal From Sleep**

Arousal is an important defense mechanism in response to upper airway obstruction. The major stimulus for arousal in response to a respiratory stimulus appears to be mechanoreceptor stimulation and the level of respiratory effort.217,218 However, this is not the only mechanism, as in patients with absent respiratory sensation, such as children with congenital central hypoventila-
tion syndrome or adults with quadriplegia, exogenous hypercapnia can cause arousal from sleep without an increase in respiratory effort.219,220

The arousal response to obstructive apnea differs markedly between children and adults. In adults, obstructive apnea termination is associated with American Sleep Disorders Association cortical arousal in approximately 70% of non-rapid eye movement (REM) events,221,222 whereas in children, arousals frequently do not occur. McNamara and colleagues223 studied infants (<21 weeks of age) and children (1-14 years of age) with OSAS. In the children, 51% of non-REM obstructive apneas terminated in electroencephalographic arousals (defined as being 1 second or longer in duration), although during REM sleep, only 35% of obstructions terminated in arousal. In the infants, only 18% of quiet (non-REM) sleep obstructions terminated in arousal and 12% of active (REM) sleep obstructions. Arousals were much less likely to occur with central apnea: 16% of central apneas were associated with arousal from non-REM sleep in children and 5% in infants.

The lack of cortical arousal in children with OSAS may explain why children can go on to have extended uninterrupted periods of obstructive hypoventilation (Figure 5).7 Because children with OSAS often do not arouse in response to obstructive apnea, sleep architecture is preserved in these patients215 and daytime sleepiness is uncommon.224 Infants with apnea, however, may have decreased REM time.225

Although children may not manifest cortical arousals, there is evidence that they do have a subcortical central nervous system or autonomic response to most obstructive apneas. Analysis of spectral electroencephalogram characteristics has shown changes during obstructive apneas.226 Several studies have shown that the vast majority of obstructive apneas in children terminate with movement, even in the absence of electroencephalogram arousals.223,227,228 Katz et al229 studied the pulse transit time, an indicator of autonomic function, in children. They demonstrated that electroencephalogram arousals occurred with 55% of obstructive apneas, similar to the results shown by McNamara, but that pulse transit time arousals occurred with 91% of obstructions. Thus, it appears as if there is subcortical activation of the brain in children in response to upper airway obstruction. It is possible that these subcortical arousals account for some of the autonomic abnormalities seen in children with OSAS and may also contribute to the neurobehavioral sequelae of this syndrome.

Why do children often not have cortical arousals to obstructive apnea? Several possibilities exist: (1) children in general have a higher arousal threshold to all stimuli, (2) children have a higher

![Figure 5](https://academic.oup.com/sleep/article-lookup/doi/10.1093/.sleep/27.5.1009)
arousal threshold to respiratory stimuli, and (3) children with OSAS have a deficit in arousal that is not seen in normal children. These possibilities are discussed below.

Children have a higher arousal threshold than adults; the younger the child, the higher the arousal threshold. For example, Busby et al.230 studied awakening in response to a 120-dB acoustic stimulus in young children (5-7 years of age), preadolescents (8-12 years of age), adolescents (13-16 years), and adults. Children awoke in 43% of trials, preadolescents in 54%, adolescents in 72%, and adults in 100%. In a separate study, 82% of infants awoke at 120 dB231; however, as different methods were used, these results might not be directly comparable to those of the older subjects. Consistent with the higher arousal threshold noted in children and adolescents, the number of spontaneous arousals during sleep increases with age, from childhood to the elderly.215,222,232

Age-related changes in the arousal threshold, however, do not appear to be the sole reason for the lack of arousal in pediatric patients with OSAS. Studies have shown that children with OSAS also have a specific arousal deficit in response to respiratory stimuli when compared to age-matched controls. This has been demonstrated using both hypercapnia and inspiratory resistive loading. The arousal response to exogenous hypercapnia and hypoxemia was studied in school-aged prepubertal children with OSAS compared to controls.198 It was found that hypoxemia (SaO2 of 75%) was a poor stimulus to arousal in both children with OSAS and normal controls, as it is in normal infants233 and normal adults.234,235 In contrast to hypoxia, hypercapnia was a potent stimulus to arousal, resulting in arousal in all subjects. This is similar to findings in other age groups. Normal infants236 and adults235,237 as well as children219 and adolescents,238 arouse to hypercapnia, although the arousal thresholds differ: end-tidal PCO2 of 52 mm Hg in infants,236 59 mm Hg in prepubertal children,198 46 mm Hg in adolescents238 and 49 mm Hg in adults.235 However, children with OSAS awoke at a higher PCO2, during both the hypercapnic and hypoxic hypercapnic challenges, compared to controls. Those with the highest apnea index had the highest arousal threshold. The hypercapnic arousal threshold decreased following treatment, suggesting that the blunted arousal threshold was secondary to chronic nocturnal hypercapnia. Children with OSAS also have a blunted arousal response to inspiratory resistive loading.205 Thus, it is possible that children with OSAS do not arouse in response to respiratory derangements and thus prevent sleep fragmentation at the expense of incurring gas exchange abnormalities. Preliminary data suggest that children with OSAS do have normal arousal responses to acoustic stimuli,239 suggesting that the arousal deficit is specific to respiratory stimuli. It is not known whether this arousal deficit is a cause or consequence of OSAS. However, one study in infants showed an increase in the arousal response to apnea following continuous positive airway pressure therapy, suggesting that the blunted arousal threshold may be secondary.240

Upper Airway Neuromotor Tone

Although the overall ventilatory drive appears to be normal in children with OSAS, it is possible that central augmentation of upper airway neuromotor function is abnormal. The upper airway muscles are accessory muscles of respiration and, as such, are activated by stimuli such as hypoxemia, hypercapnia,241 and upper airway subatmospheric pressure.242 Previous studies have shown that, when upper airway muscle function is decreased or absent, eg, in postmortem preparations,243 the airway is prone to collapse. Conversely, stimulation of the upper airway muscles with hypercapnia244 or electrical stimulation245 results in decreased collapsibility. These studies confirm that the tendency of the upper airway to collapse is inversely related to the level of activity of the upper airway dilator muscles. Therefore, increased upper airway neuromotor tone may be one way that patients can compensate for a narrow upper airway. Indeed, this has been shown in adults. Mezzanotte and colleagues1 demonstrated that adult patients with OSAS compensated for their narrow upper airway during wakefulness by increasing their upper airway muscle tone. This compensatory mechanism was lost during sleep.2 Recently, Katz and White246 performed similar studies in children, using intraoral electrodes. Children with OSAS had greater genioglossal EMG activity (expressed as percentage of maximal awake activity) during wakefulness than controls and a greater decline in EMG activity during sleep onset. During stable nonREM sleep, EMG activity remained below the waking baseline in the controls but increased above the baseline in a few of the subjects with OSAS, suggesting the presence of a compensatory mechanism in some individuals.

During REM sleep, upper airway motor tone decreases. EMG activity during REM sleep in OSAS has not been well studied due to practical difficulties, but this would be key as obstruction occurs so frequently during REM sleep. In children, in particular, obstructive apnea occurs predominantly during REM sleep, suggesting a prominent role of neuromotor factors. In one study, 56% of obstructive apneas in children occurred during REM sleep, although REM sleep accounted for only 22% of total sleep time.215 In contrast, in the same institution, 33% of obstructive apneas in adults occurred during REM, which was 17% of total sleep time (personal communication from Naresh Punjabi).

Measurement of upper airway pressure-flow relationships provides a noninvasive means of evaluating upper airway function during sleep.247 In the living organism, the upper airway pressure-flow relationship is affected not only by mechanical and structural factors, but also by neural mechanisms. Thus, these measurements provide a useful tool for the comprehensive evaluation of upper airway function. Upper airway pressure-flow measurements can be obtained by having the sleeping patient wear a nasal mask attached to a pneumotachometer, for the measurement of inspiratory airflow. Pn is measured from a mask port. Pn is then gradually altered through a range of positive and negative (subatmospheric) pressures. Pressure-flow curves are constructed by plotting maximal inspiratory airflow (Vmax) of flow-limited breaths against Pn. Only flow-limited breaths are used because, in the flow-limited condition, Vmax is determined solely by the upper airway properties and is independent of the pressure downstream from the collapsible locus of the upper airway.247 Pn versus Vmax curves are fitted by least squares linear regression. The Pcrit is defined as the X-axis intercept of the regression line, ie, the Pn at which there is zero airflow. The slope of the curve has also been used to characterize upper airway function, with a flat slope representing a decreased tendency for the upper airway to collapse.200

Original work in adults, both normals and those with sleep-disordered breathing, have shown that the pressure-flow curve has a
steep slope with a discernible $P_{\text{crit}}$. $P_{\text{crit}}$ is greatest in adults with obstructive apnea and is in the positive range, suggesting that the upper airway will collapse during normal atmospheric breathing.247,248 $P_{\text{crit}}$ then progressively decreases to more and more negative (subatmospheric) levels in adults with hypopnea, primary snoring, upper airway resistance syndrome, and normals.248,249 In children with OSAS, $P_{\text{crit}}$ is in the positive range, similar to that of adults with OSAS.19 In contrast, children with primary snoring have markedly subatmospheric $P_{\text{crit}}$ values, lower than those seen in adults with primary snoring.19 Normal children have an even less collapsible airway. Experiments have shown that most normal nonsnoring children are able to maintain their inspiratory flow rates even at markedly subatmospheric pressures.200 Thus, as nasal pressure decreases, inspiratory flow is maintained, presumably due to an increase in upper airway neuromotor tone (Figure 6). Thus, the X intercept of the pressure-flow curve cannot be determined without extreme extrapolation and, consequently, $P_{\text{crit}}$ cannot always be determined. Therefore, the slope of the pressure-flow curve (the reciprocal of the resistance upstream to the collapsible locus in the upper airway) has been used to characterize the upper airway response. Further experiments in infants have shown that the normal infant airway, like that of the prepubertal child, is resistant to collapse during natural sleep250 (Figure 7). Thus, normal nonsnoring infants and children have a less collapsible upper airway than do adults. Currently, studies are being performed in adolescents to determine at which point the transition from the pediatric to the adult pattern occurs.

In contrast to these dynamic studies of the upper airway, Isono and colleagues65,251 have studied the static mechanical properties of the passive pharynx. With the use of endoscopy, they measured the pressure-area relationship of the upper airway in infants, children, and adults undergoing general anesthesia with complete skeletal muscle paralysis. They found that anesthetized paralyzed children with OSAS had a positive passive closing pressure of the upper airway that was slightly lower than that of adults studied using the same technique. Of interest, however, was that their normal control children had a lower closing pressure (less collapsible upper airway) than either the normal adults or normal infants studied (Figure 7).252 Thus, in studies of both the passive and active airway, children have a less collapsible upper airway than do adults. This suggests that normal children have anatomic, structural, or both anatomic and structural factors (eg, differences in wall stiffness) minimizing the tendency for the airway to collapse. In infants, the difference between the passive and active states suggests that upper airway neuromotor tone plays an important role in maintaining airway patency during sleep in this age group. This is supported by studies showing that the upper airway closing pressure in infants is higher in postmortem preparations than during natural sleep.243,253 As with the dynamic studies, passive studies of the upper airway show increased collapsibility in both children and adults with OSAS compared to controls, consistent with the theory that anatomic factors, in addition to neuromotor factors, are very important in the pathogenesis of OSAS.

The dynamic and passive techniques are quite different from each other, as one measures the changes in flow in response to changes in upper airway pressure, whereas the other measures the changes in area. Therefore, it may not be valid to directly compare results from one technique to that of the other. Nevertheless, the 2 techniques are analogous. Thus, it is interesting to note that the $P_{\text{crit}}$ in the dynamic airway is much lower than in the passive airway. This supports the contention that upper airway neuromotor tone is important in maintaining upper airway patency.

Upper airway neuromotor reflex responses have been examined in children and adults. During wakefulness, adults with OSAS demonstrate a decrease in genioglossal EMG when exposed to hypoxemia,254 whereas normal subjects demonstrate an increase.255 Similar studies have not been performed in children, although one case was reported where a child with OSAS developed upper airway obstruction during wakefulness while undergoing hypoxic ventilatory response testing.197 In normal

![Figure 6](https://example.com/figure6.png)

**Figure 6**—Maximal inspiratory flow ($V_{\text{max}}$) versus nasal pressure ($P_{\text{N}}$) is plotted for a 42-year-old adult (panel A) and a 6-year-old child (panel B). In the adult, $V_{\text{max}}$ decreases as $P_{\text{N}}$ became more negative. Critical closing pressure ($P_{\text{crit}}$) is -21 cm H$_2$O, and the slope of the upstream-pressure/flow curve is steep (22 ml/second per cm H$_2$O). In the child, $V_{\text{max}}$ is maintained despite increasing subatmospheric $P_{\text{N}}$; thus, $P_{\text{crit}}$ could not be determined. The slope of the upstream-pressure/flow curve is flat (2 ml mL/second per cm H$_2$O). Reproduced from Marcus CL, Lutz J, Hamer A, Smith PL, Schwartz A.200

![Figure 7](https://example.com/figure7.png)

**Figure 7**—The critical closing pressure ($P_{\text{crit}}$)/closing pressure of the upper airway (circles) and the slope of the upper airway pressure-flow curve (triangles) are plotted for different age groups. Panel A shows the dynamic airway and panel B the passive airway. In the passive state, the prepubertal child has a less collapsible upper airway than either the infants or adults, whereas in the dynamic state, both infants and children have a less collapsible upper airway than adults.65,250-252,265 Note that $P_{\text{crit}}$ values were calculated using a lower cutoff value of -25 cm H$_2$O.
adults, there is a brisk upper airway response to both exogenous CO₂ and negative pressure during wakefulness but little response during sleep. In contrast, normal children have a brisk upper airway response to CO₂ and negative pressure during sleep. The upper airway responses to CO₂ and negative pressure are similar, which is consistent with the knowledge that upper airway receptors for negative pressure appear to be the same as those for CO₂ although they are separate from receptors for other stimuli such as cold, airflow, and irritants.

The upper airway response in infants has been studied using different techniques from those used for older subjects, and many of the studies have been performed in premature rather than full-term infants. Gauda et al demonstrated a rapid upper airway EMG response to upper airway occlusion in premature neonates; Carlo et al found similar results. Based on these studies, it is most likely that infants have active upper airway responses during sleep but that the mechanism and timing of these responses differ from the older age groups.

These studies of upper airway function showing that pediatric subjects have a less collapsible upper airway than adults, and brisker upper airway reflexes, are borne out by our clinical knowledge that normal children snore less than adults and rarely have any obstructive apneas during sleep. Why is the normal pediatric airway less collapsible than that of the normal adult? Many factors regulate upper airway function, including central ventilatory drive, chemoreceptor afferents, upper airway pressure and flow receptors, pulmonary mechanoreceptors, posture and neck position, changes in lung volume, and sleep state. Several studies have confirmed that the central nervous system plays an important role in preserving upper airway patency. As stated earlier, the upper airway muscles are activated by stimuli such as hypoxemia, hypercapnia, and subatmospheric pressure loads. The following facts suggest that the upper airway activation in response to pressure loading is centrally mediated: (1) humans respond very differently to upper airway loading during sleep compared to wakefulness suggesting a role for the higher central nervous system centers; (2) functional MRI studies show activation of central nervous system centers in response to upper airway loading; and (3) the EMG responses of the upper airway muscles to hypercapnia and inspiratory loading are similar. These studies suggest a role for the central nervous system in modulating the upper airway response to subatmospheric pressure. As previously noted, children have a higher ventilatory drive than adults, and the ventilatory drive during sleep correlates with the slope of the pressure-flow curve. Thus, normal children may compensate for a relatively narrow upper airway by increasing upper airway neuromotor tone, via an increased central ventilatory drive.

In children with OSAS, upper airway responses to CO₂ and negative pressure during sleep are diminished. It is not known whether this diminished response is a primary cause of OSAS or whether it is secondary, ie, due to habituation to chronic hypercapnia during sleep.

**Upper Airway Sensation**

The afferent (sensory) loop of the upper airway negative pressure reflex also plays a role in promoting airway stability. During wakefulness, topical nasopharyngeal anesthesia in adults results in increased upper airway collapsibility in both children and adults. Similarly, during sleep, the application of topical nasopharyngeal anesthesia in adults results in increased upper airway collapsibility, leading to obstructive apnea. The resultant worsening of apnea appears to be due, at least in part, to changes in muscle tone but also to blunting of the arousal response.

There also appears to be a defect in upper airway sensation in adult patients with OSAS. A number of studies have shown decreased pharyngeal sensation in response to stimuli such as temperature, touch, and vibration. It is speculated that this is due to sensory nerve damage secondary to vibrational trauma from years of snoring. Similar studies have not been performed in children. It is possible that children have normal upper airway sensation, due to the shorter duration of snoring in these patients.

**Summary of Neuromotor Factors**

In summary, the overall ventilatory drive in response to hypoxia and hypercapnia is probably normal in otherwise-healthy OSAS patients of all ages (although infants have a strong biphasic response to hypoxemia and are more likely to develop central apnea when exposed to prolonged hypoxemia). However, the central ventilatory drive plays a role in augmenting upper airway neuromotor reflexes and tone. Normal infants and children have brisker upper airway reflexes during sleep than do adults, perhaps due to their greater central ventilatory drive. These reflexes appear to be blunted in children with OSAS; it is not known whether this blunting is a primary or secondary phenomenon.

Children and infants are less likely to arouse in response to upper airway obstruction than are adults. Unlike adults, children and infants do not compensate for prolonged increases in inspiratory resistive load. This may explain why patients in the pediatric age group often have obstructive hypoventilation rather than discrete, cyclic obstructive apneas.

**PROGNOSIS OF CHILDHOOD OSAS**

The natural course and long-term prognosis of childhood OSAS are unknown. Specifically, it is not known whether childhood OSAS is a precursor of adult OSAS or whether these are two diverse diseases affecting discrete populations. There are very few longitudinal studies of childhood OSAS. Guilleminault and colleagues reevaluated adolescents who had been successfully treated with adenotonsillectomy during childhood. There were 49 subjects, of whom 23 returned for reevaluation. Of these, 5 snored and 3 (13%) had recurrence of OSAS. All patients with recurrence were male. In one other long-term study, 20 of 61 children who had undergone adenoidectomy and/or tonsillectomy as treatment for OSAS were reevaluated as adolescents. Subjects were studied overnight using pulse transit time, pulse oximetry, and a microphone. Subjects with previous OSAS were found to have more snoring and greater inspiratory effort (as measured by pulse transit time) during sleep than controls. Both of these studies can be criticized for methodologic problems, such as obtaining subjects retrospectively, lack of follow-up of all potential subjects, lack of evaluation for possible adenoidal regrowth, and incomplete diagnostic techniques. However, they do suggest that a subsection of children with OSAS may be at risk for occurrence of the disease in later life. This is supported by some small physiologic studies showing residual abnormalities in upper airway...
collapsibility in prepubertal children with OSAS following adenotonsillectomy. Thus, it can be theorized that some children with OSAS have subtle abnormalities of central ventilatory control or upper airway neuromotor tone or have predisposing anatomic factors other than adenotonsillar hypertrophy. These abnormalities may be clinically inapparent until the adenotonsillar hypertrophy results in an increased mechanical load on a marginal upper airway, thus precipitating OSAS. Following surgical treatment, patients may again become asymptomatic. However, it is possible that these high-risk children will develop a recurrence of OSAS during adulthood if they acquire additional risk factors, such as weight gain, or androgen secretion at puberty. Well-designed, large-scale, long-term epidemiologic studies are needed to confirm this hypothesis.

**RESEARCH QUESTIONS**

There are many pressing unanswered questions regarding the developmental pathophysiology of OSAS. In particular:

- What is the pathophysiology of the “idiopathic” OSAS often seen in infants?
- What is the natural history of childhood OSAS? Is childhood OSAS a precursor of adult OSAS, or a separate disease process? If the former, what is the recurrence rate during later life? What are the risk factors for recurrence?
- What is the effect of childhood OSAS on craniofacial growth and structure? Does adenotonsillar hypertrophy result in craniofacial changes that could result in obstructive apnea later in life or is the apparent adenotonsillar hypertrophy a result of overcrowding from a narrower upper airway? What is the potential role of treatments such as intraoral appliances and rapid maxillary expansion in changing craniofacial growth in children?
- What is the relative contribution of obesity to childhood upper airway function, and how does this differ from adults?
- Are the blunted arousal and upper airway neuromotor response in children with OSAS a primary deficit or are they secondary to chronic respiratory abnormalities, sleep disturbances, or both?
- When does the childhood pattern of OSAS transition into the adult pattern? What are the effects of puberty on upper airway function and structure?
- What role do genetic, ethnic, and anthropometric factors play in the pathophysiology of OSAS?
- What are the contributions of repeated asphyxia versus sleep fragmentation on the neuromechanical determinants of upper airway patency?

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