

Developmental Aspects of the Upper Airway

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The upper airway serves three important functions: respiration, swallowing, and speech. During development it undergoes significant structural and functional changes that affect its size, shape, and mechanical properties. Abnormalities of the upper airway require prompt attention, because these often alter ventilatory patterns and gas exchange, particularly during sleep when upper airway motor tone and ventilatory drive are diminished. Recognizing the relationship of early life events to lung health and disease, the National Heart, Lung, and Blood Institute (NHLBI), with cofunding from the Office of Rare Diseases (ORD), convened a workshop of extramural experts, from many disciplines. The objective of the workshop was: (1) to review the state of science in pediatric upper airway disorders; (2) to make recommendations to the Institute to fill knowledge gaps; (3) to prioritize new research directions; and (4) to capitalize on scientific opportunities. This report provides recommendations that could facilitate translation of basic research findings into practice to better diagnose, treat, and prevent airway compromise in children.

The NHLBI convened a pediatric strategic planning work group in July 2008 to review and make recommendations for priority future directions in pediatric respiratory biology and disease. This group identified the lack of knowledge regarding development and growth of the upper airway. Although the developmental biology portfolio in the Division of Lung Diseases has made significant contributions to the understanding of lung and lower airway development, science to address the upper and large airways is lacking. Therefore, NHLBI convened a workshop in March 2009 with co-sponsor, Office of Rare Diseases, NIH, attended by clinicians and scientists from diverse fields in health-

care and the biological sciences, to determine research questions and areas of priority related to the pediatric upper airway.

The upper airway, defined as the air-conducting passages from the level of the nose to the carina, is susceptible to congenital and acquired abnormalities that affect up to 3% of the pediatric population (1). The upper airway serves the primary purposes of respiration, deglutition, clearance of secretions, separation of nasal and oral passageways, and phonation. These vital functions often occur simultaneously, requiring precise coordination of its multiple anatomical subcomponents. Not uncommonly, infants and children present with multiple levels of upper airway anomalies and incoordination, creating a challenging diagnostic and treatment dilemma. The range of upper airway anomalies is broad and can include a combination of morphologic, neuromuscular, mucosal, bony, and cartilaginous deficits. Inherent to upper airway anomalies is a high morbidity and mortality, need for specialized chronic care, disproportionate allocation of resources, and a poor quality of life. Intensive care units for neonates and children care for an increasing number of children with these types of airway problems. Treatment options for upper airway anomalies are most commonly surgical, may only provide a partial restoration of function, and often create other short- and long-term morbidities. While these treatment options are helpful, they do not typically address the underlying pathophysiology. The advancement of effective intervention remains limited by a lack of knowledge regarding molecular and pathophysiologic mechanisms of development, growth, and the response of tissues to injury. In the following sections, we review the known developmental aspects of the upper airway and outline potential areas of investigation with the ultimate goals of improved patient care, quality of life, and decreased financial burden to society. Priority areas for research are presented. These areas were selected because they are highly relevant to clinical disorders associated with abnormal upper airway function, and because a focused research effort would rapidly advance our understanding of the area. However, it is recognized that these priority areas are not exclusive.

CRANIOFACIAL AND LARYNGOTRACHEAL AIRWAY DEVELOPMENT

Background

Knowledge regarding the environmental, genetic, protein and cellular interactions involved in the organization of the

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complex tissues comprising the upper respiratory tract is relatively undeveloped compared with that in other organ systems. Malformations and injuries to the upper airway are relatively frequent, often necessitating extensive reconstructive surgery and prolonged medical, surgical and ventilatory support. Knowledge regarding the development and functional properties of the upper airway will provide a platform for the creation of more effective interventions and strategies that may be used to enhance repair and recovery from these disorders.

PRIORITY AREA 1: Define the Epidemiology, Natural History, Genetic and Epigenetic Basis of Syndromes that Impact the Upper Airway, with the Goal of Understanding the Molecular Biology of Normal and Abnormal Upper Airway Development

The reported incidence of congenital airway anomalies in infants who present with respiratory insufficiency ranges from 37 to 85% (2–6). The epidemiology, natural history, and genetics for disorders affecting the upper airway are largely unknown. This lack of knowledge hinders the ability to understand risk factors for upper airway anomalies, long-term sequelae of upper airway anomalies and of surgical interventions on the upper airway, and efficacy of different treatment options. Furthermore, without a molecular understanding of normal and abnormal upper airway development, it is difficult to design better diagnostic and treatment paradigms for children with upper airway anomalies. To address this knowledge deficit, a network must exist among clinicians to prospectively acquire standardized data sets and genetic material from children with airway anomalies as well as maintain an infrastructure to analyze this information. Furthermore, to define abnormal upper airway anatomy and function, age-stratified normative data from nonaffected children must be established.

Development of the midface. The nose, maxilla and mandible form early during human embryogenesis with large contributions from lateral plate mesoderm and from neural crest (7–11). The nasal placodes give rise to nasal development around the fifth week. Concomitantly, the primary palate is formed during the fusion of the medial nasal prominences with the frontonasal prominence. Later, the secondary palate forms as outgrowths of the maxillary arches which then extends, elevates and fuses during the seventh week. For palatal shelf elevation and fusion to occur, the mandible must lengthen and draw the tongue downward, away from the fusion plane of the secondary palatal shelves. Final facial morphology separates the nasal and the oral airways. Interruption of any of these processes leads to craniofacial anomalies and secondarily affects the upper aerodigestive tract. The growth of the craniofacial skeleton is impacted by the functional status of each sub-component, and the coordinated adjustment of all tissues (7, 8, 10).

Development of the oropharynx and hypopharynx. The configuration and function of the tongue largely dictates the patency of the oropharyngeal and hypopharyngeal airway. Development of tongue musculature originates from paraxial somites, in contrast to the rest of the head and neck musculature, which develops from somitomeres. The myogenic cells migrate to the mandible under the influence of hepatocyte growth factor (HGF), where insulin-like growth factor-1 (IGF-1) promotes the differentiation into myoblasts (11). In mice, myogenesis and synaptogenesis of the tongue muscles proceed faster than those of the limbs and masticatory muscles, ending at birth. The more rapid functional development of the tongue likely facilitates the early feeding pattern of suckling, as opposed to chewing, which is required later in life. Sonic hedgehog (SHH) is thought to play a key role in the development and differen-

TABLE 1. GENETIC ETIOLOGY

| Phenotype/Syndrome | Genetic Etiology |
|---|---|
| Small mandible (Pierre Robin Sequence) | Multiple candidate genes including GAD67, PVRL1, SOX9, COL2A1, COL11A1, and COL11A2 |
| Glottic web (Velocardiofacial syndrome) | 22q11.2 deletion |
| Elliptical cricoid | Unknown |
| Laryngeal cleft/ tracheoesophageal fistula | MID1, and undefined gene on chromosome 22 |
| Complete tracheal rings | Unknown |
| Tracheal cartilaginous sleeve (Pfeiffer, Apert, Crouzon) | FGFR mutation |
| Subglottic stenosis (Down Syndrome) | Trisomy 21 |

tiation of the tongue, as disruption of SHH can significantly alter morphology and differentiation of tongue tissue in mice (9).

Abnormal differentiation of tongue musculature likely underlies tongue abnormalities associated with obstructive disorders. For example, in Pierre-Robin sequence (PRS), differentiation of tongue musculature is thought to be delayed. The reduced muscular activity associated with delayed tongue development then results in decreased mandibular growth and a failure of the palatal shelves to rotate properly, leading to a palatal cleft (10). Therefore, studies have shown a correlation between mandible length and severity of the palatal cleft in PRS (7).

In addition to abnormal differentiation of the tongue, inherited anomalies of craniofacial structure and neuromotor development can contribute to obstructive apnea in the awake or sleeping state. Underdevelopment of the maxilla can reduce the oropharyngeal airway, leading to upper airway obstruction. Retrusion of the maxilla and mandible can be seen in PRS, Apert's and Treacher Collins syndromes, among others. Macroglossia (e.g., in Beckwith Wiedemann and Down syndrome) and hypotonia (e.g., in Prader Willi and Down syndrome) can also contribute to significant upper airway obstruction. Abnormalities of ventilatory control will further exacerbate the condition.

Development of the supraglottis, glottis, subglottis, and trachea. Commonly occurring congenital anomalies of these regions include laryngomalacia, tracheomalacia, subglottic stenosis, glottic web, vocal cord paralysis, tracheal stenosis, laryngeal clefts, tracheoesophageal fistula, and subglottic hemangioma (2–6). The genetic etiology for some of these congenital anomalies is at least partially known (Table 1). Important to note is that many of these congenital anomalies involve mainly the cartilaginous support structure of the upper respiratory tract (12) (Table 2), while others are due to a combination of cartilaginous, soft tissue, and neuromuscular abnormalities.

The cartilaginous support structure represents a key sub-element of the upper airway, providing the integrity to keep the laryngeal and tracheal lumens patent, and providing attachments for associated muscles. The laryngeotracheal skeleton is made up of several cartilaginous structures strung together in

TABLE 2. DEFECTS IN CARTILAGINOUS SUPPORT STRUCTURE

| Congenital Anomaly | Description of Defect |
|-------------------------|--|
| Laryngomalacia | Cartilaginous support structures of larynx lack integrity Likely abnormal neuromuscular input |
| Tracheomalacia | Foreshortened and/or weak tracheal rings |
| Subglottic stenosis | Elliptical or small cricoid ring |
| Laryngeal cleft | Defect in posterior lamina of cricoid ring |
| Complete tracheal rings | Tracheal cartilage rings form complete rings |

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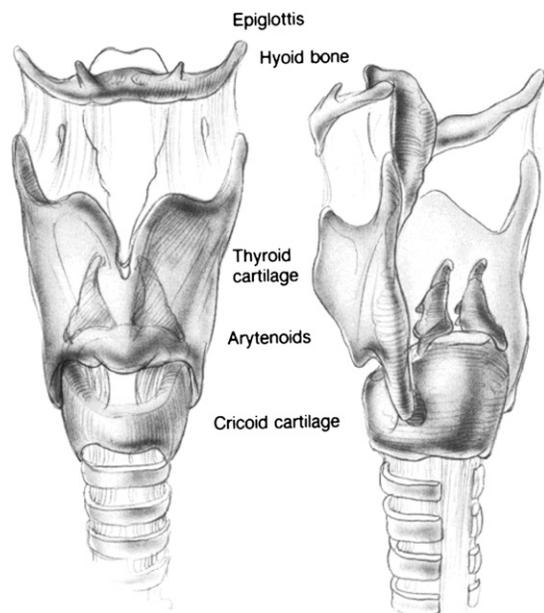


Figure 1. Normal anatomy of the cartilaginous framework of the supraglottic, glottic, and subglottic regions. The cartilage in this region maintains structural support and luminal airway patency. Adapted by permission from Reference 65.

series and suspended from the skull base and mandible (Figure 1). A detailed description of the anatomy of the cartilaginous support structures of the larynx and trachea can be found in Hollinshead (13). The current understanding of the embryology of the larynx and trachea is limited to descriptive anatomic studies in the mouse and postmortem studies in human embryos (14–21).

Acquired upper airway abnormalities. The second broad category of upper airway disorders, acquired airway anomalies, most frequently results from prolonged intubation and/or airway instrumentation resulting in inflammation, scarring, and resultant narrowing. Common acquired upper airway abnormalities include tracheal and subglottic stenosis. The exact rate of occurrence of acquired airway anomalies is unknown, but has increased because of the improved survival of premature infants who require prolonged intubation for ventilatory support. Histologic examination of stenotic segments often reveals a combination of luminal soft tissue thickening with concomitant cartilaginous deformity (thickening or ring fracture with loss of structural support) (15, 16, 22). Current investigation into the field of subglottic/tracheal luminal growth suggests a role for epithelial-driven expansion of the underlying cartilage (23). Mechanisms of cartilage growth may

not only involve epithelial–mesenchymal interactions but also extracellular matrix remodeling by matrix metalloproteinases located predominantly at the intraluminal surface of the cartilage rings (24). Inflammation and erosion in this location could theoretically disrupt the process of well-coordinated luminal expansion.

Research opportunities/questions

1. Identify genetic and environmental risk factors for upper airway anomalies by developing appropriate metrics for phenotyping in support of genome wide association studies and copy number variation analysis in gene × gene and gene × environment assessments.
2. Develop methodologies for early genetic testing for risk factors for upper airway anomalies.
3. Understand the contribution of anatomic, pathologic, inflammatory, and neurologic factors in causing upper airway obstruction.
4. Characterize the natural history of upper airway anomalies, associated morbidities, and the role of early intervention in reducing morbidities.
5. Develop algorithms for reducing environmental risk factors for upper airway anomalies.
6. Develop regenerative methods for restoring the upper airway using gene-, cell-, and tissue-based approaches.
7. Research quality of life and healthcare allocation for patients with upper airway anomalies.

PRIORITY AREA 2: Creation of Animal Models to Aid in the Understanding of both Congenital and Acquired Upper Airway Anomalies

Using genetically engineered mouse models, multiple key signaling pathways have been implicated in the development of the upper airway. Many of these animal models approximate upper airway anomalies found in infants. For example, cleft palate has been identified in transforming growth factor β3 (TGF-β3)–null mice, midface anomalies are associated with fibroblast growth factor (FGF) mutations, and mice trisomic for orthologs of genes on human chromosome 21 replicate the midface and mandibular hypoplasia of Down syndrome, starting with anomalies of neural crest development. Abnormal expression of SHH has been associated with glossoptosis, pyriform aperture stenosis, tracheoesophageal fistula, and/or laryngotracheoesophageal cleft malformations (25). Multiple other cytokines and transcription factors have been implicated in upper airway anomalies (Table 3) (26–34). It is likely that other mouse models display upper airway abnormalities that have not been identified due to lack of screening by investigators with appropriate knowledge. Under-

TABLE 3. SUMMARY OF GENES ESSENTIAL FOR NORMAL TRACHEOESOPHAGEAL DEVELOPMENT

| Gene | Mutant Phenotype | Human locus |
|--|--|--------------------------|
| RARα ^{-/-} ;RARβ ₂ ^{-/-} or RARα ₁ ^{-/-} ;RARβ ^{-/-} | Tracheoesophageal fistula, lung hypoplasia, or agenesis | RARα:17q21.1, RARβ: 3p24 |
| Shh ^{-/-} | Esophageal atresia, tracheoesophageal fistula, lungs form rudimentary sacs | 7q36 |
| Gli2 ^{-/-} ;Gli3 ^{+/-} | Esophageal atresia, tracheoesophageal fistula, severe lung phenotype | Gli2; 2q14, |
| Gli2 ^{-/-} ;Gli3 ^{-/-} | No formation of esophagus, trachea, and lungs | Gli3:7p13 |
| Foxf1 ^{-/-} | Lethal before Embryonic Day 10, extra-embryonic defects | 16q24 |
| Foxf1 ^{+/-} | Esophageal atresia, tracheoesophageal fistula, lung immaturity and/or hypoplasia, lobulation defects | |
| TTF-1 ^{-/-} | Tracheoesophageal fistula, rudimentary peripheral lung primordia | 14q13 |
| HoxC4 ^{-/-} | Partially or completely blocked esophageal lumen, disruption of esophageal musculature | 12q13.3 |
| Tbx4 misexpression | Tracheoesophageal fistula | 17q21-q22 |

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standing the pathways, genes, and processes involved in normal upper airway morphogenesis and growth will be required to understand the pathogenesis of upper airway anomalies. Furthermore, a molecular understanding of normal and abnormal upper airway development will allow the development of genetic tests for earlier identification of upper airway anomalies, and genetic and cell-based therapies to regenerate normal upper airway. The genes identified in these studies represent potential targets for therapeutic intervention.

Research opportunities/questions

1. Development of mouse models for the study of upper airway anomalies. This might include appropriate screening of existing models as well as creation of new models to identify novel gene interactions responsible for abnormal upper airway development.
2. Define key genes, growth factors, and cell populations (e.g., neural crest or mesoderm-derived cells) that are determinants of normal airway development. Characterize their spatial and temporal distribution in the developing upper airway.
3. Develop additional model systems for the study of upper airway anomalies. Larger animal models may provide the ability to study aberrant growth, injury, and interventions.
4. Develop gene-, cell-, and tissue-based paradigms to restore, heal, and/or regenerate normal upper airway.

PRIORITY AREA 3: Prevention of Iatrogenic Injury and Improvement of Treatment Strategies for Upper Airway Anomalies

Current prevention and treatment protocols for upper airway anomalies, either congenital or acquired, are often developed based on anecdotal information or limited scientific review. Some surgical interventions themselves can be associated with significant long-term morbidities. For example, timing of mandibular advancement is based on limited scientific data, and there is therefore potential for long-term disruption of the growth and function of the mandible (35). Similarly, there are limited long-term data on the efficacy and associated morbidities of tracheal reconstruction and tracheotomy. To create more effective treatment interventions and limit secondary injury, it is necessary to understand the effect of upper airway surgery on normal growth and development.

Research opportunities/questions

1. Characterization of the long-term outcomes of upper airway surgery (cleft lip and palate repair, midface advancement, surgical treatment of obstructive sleep apnea, supraglottoplasty, treatment of vocal fold movement disorders, treatment of neoplasms of the upper airway, intubation, tracheotomy, etc.) that may have long-term complications.
2. Establishment of best-practice guidelines outlining diagnostic work-up, timing of intervention, and type of treatment intervention for each specific commonly encountered upper airway anomaly.
3. Development of animal models to study the response of the upper airway to commonly applied airway surgeries.

DEVELOPMENT OF UPPER AIRWAY NEUROMOTOR CONTROL

Background

Upper airway function is highly complex, and requires rigorous coordination to achieve competing functions, each critical for

life. The neural system regulating upper airway function must successfully enable breathing, feeding (suckling, swallowing, etc.), and vocalizing. Although remarkable advances have been made in neuroscience during recent years, relatively little is known concerning neural control of the upper airway during normal development. We know even less concerning airway neuromotor control in children with clinical disorders that affect the upper airways and their development.

PRIORITY AREA 1: Developmental Plasticity in Upper Airway Control

Plasticity is a fundamental property of neural systems, including the neuromotor system controlling breathing and upper airway function (36). Plasticity is defined as a persistent change in neuromotor function induced by prior experience, such as altered neural activity, intermittent hypoxia, hyperoxia, pharmacologic or therapeutic interventions, and disease or injury. Although plasticity is observed in animals of all ages, some forms are unique to development. Such *developmental plasticity* is induced by experiences that occur only during critical developmental periods, whereas similar experiences not in that critical period have no lasting effects (37, 38). Although developmental plasticity guides normal neural development, inappropriate experiences during the critical “window” may induce maladaptive plasticity, potentially contributing to diseases later in life. Our recognition that developmental plasticity plays an important role in ventilatory control is relatively new, and few (if any) studies have focused on developmental plasticity in neural control of the upper airway. Thus, there are significant gaps in our understanding of the potential role played by maladaptive plasticity in pediatric upper airway disorders.

Research opportunities/questions

1. How do early life experiences shape the development of neuromotor control?
2. What factors induce maladaptive plasticity? Factors that should be evaluated include: intermittent hypoxia, supplemental oxygen, abnormal circadian rhythms, impoverished environments, maternal separation stress, malnutrition, drugs of abuse (including nicotine and alcohol), and caffeine therapy for apnea of prematurity.
3. Are interventions possible to prevent/reverse maladaptive plasticity?
4. How is development of upper airway control altered by abnormal craniofacial anatomy (e.g., Down syndrome, cleft palate)?
5. Development of animal models of developmental plasticity pertinent to human infants.

PRIORITY AREA 2: Neuromotor Abnormalities: Sleep versus Wakefulness

Vigilance state has a profound impact on the neural control of breathing and the upper airway. In some disorders, breathing instability is observed during sleep (e.g., central and obstructive sleep apnea), whereas in other disorders it is more prominent during wakefulness (e.g., Rett syndrome). An important goal is to understand general principles that alter neural control in different vigilance states.

The obstructive sleep apnea syndrome (OSAS) is a common and serious cause of morbidity in children. OSAS may affect children of all ages and can lead to significant cardiovascular and neurocognitive deficits (39, 40). The prevalence of OSAS in the general pediatric population is about 2% (41). However,

several populations are at a much higher risk. These include premature infants and children with craniofacial anomalies, neurological disorders, or obesity. Although OSAS is associated with increased upper airway resistance during sleep, anatomical abnormalities do not fully explain the state-dependence of sleep-disordered breathing (42). Although the major cause for OSAS in children is considered to be adenotonsillar hypertrophy, residual OSAS persists in about 20 to 40% of children after adenotonsillectomy (43–45). This suggests that other anatomical or functional causes play an important role in the disorder. Thus, it is important to understand neuromotor compensation during sleep, and whether these mechanisms can be enhanced to minimize apneas.

Research opportunities/questions

1. What are the best methods to monitor and assess ventilatory control, respiratory effort, and arousal thresholds in infants and children?
2. What neural mechanisms regulate arousal threshold, ventilatory control instability, and compensatory respiratory plasticity in infants and children during sleep? How do these factors interact to determine airflow phenotype during sleep?
3. What is the role of neuromotor, ventilatory control, and structural factors in the pathophysiology of OSAS in infants and children? What role do contributing factors such as genetics, obesity, and infection/allergy/inflammation play?
4. Development of more effective therapies for central and obstructive apnea syndromes in infants and children, including improved pharmacological, medical, and surgical therapies.
5. What unique features lead to instability in breathing and upper airway regulation during certain states such as wakefulness and rapid eye movement sleep?

PRIORITY AREA 3: Infection/Inflammation and Neuromotor Development of the Upper Airway

Viral infections such as respiratory syncytial virus (RSV) are associated with increased severity and persistence of apneas in preterm infants (46). Since infants with persistent apnea exhibit cognitive deficits, apneas may have long-term consequences for brain function. Upper airway infections also correlate with sudden infant death syndrome (SIDS). Increased cytokine levels have been reported in the brainstems of infants who died from SIDS, suggesting a degree of brain inflammation. However, it is not known if this inflammation is a causal factor or if it is triggered by airway infections.

Little is known concerning interactions between inflammatory/immune responses and neural control of breathing or neuromotor control of the upper airway. However, the immune system has a profound impact on neural functions such as synaptic transmission and plasticity (47). Experiences frequently encountered by preterm infants, such as supplemental oxygen therapy, enhance innate pulmonary immunoregulatory responses (48). Thus, therapeutic interventions may unintentionally induce complex immune/neural interactions that underlie pathology in ventilatory and upper airway neuromotor control.

Research opportunities/questions

1. Do respiratory infections and/or inflammatory responses alter airway reflexes critical for upper airway function? Because the laryngeal chemoreflex induces central apneas to prevent aspiration, it is important to know how RSV

infection (or other immune responses) affect chemoreflex sensitivity.

2. Does respiratory infection/inflammation suppress mechanisms of compensatory plasticity that stabilize breathing after repetitive apneas (and intermittent hypoxia)? Because respiratory plasticity after intermittent hypoxia may minimize apneas during sleep (49), its loss due to infection/inflammation may predispose to sleep-disordered breathing.
3. Does supplemental oxygen exacerbate pulmonary immunoreactivity, thereby increasing the impact of subsequent infections on the laryngeal chemoreflex and compensatory respiratory plasticity?
4. Is there a causal mechanism for RSV infection in SIDS and if so, what therapeutic strategies (such as immunization) could address this?
5. Since SIDS is associated with abnormal brainstem serotonergic neurons, do immune/inflammatory interactions with serotonergic function contribute to SIDS or to sleep-disordered breathing?

PRIORITY AREA 4: Coordination of Upper Airway Functions

In neonates, protection from aspiration during feeding requires coordination of patterned motor activities that govern breathing, sucking, and swallowing. Despite complex developmental changes in the anatomical relationships between the tongue, oropharynx, palate, and larynx, we have only a rudimentary understanding of their normal and abnormal neuromotor control during development. We have little understanding of mechanisms that break down in disease states, contributing to pulmonary aspiration and/or apnea.

Research opportunities/questions

1. How are motor patterns for breathing, airway protection, feeding, and swallowing coordinated in infants and children? In adults, evidence is accumulating that upper airway sensory systems are critical in coordinating motor patterns protecting airways during swallowing.
2. Can new technologies be developed to enable real-time, bedside monitoring of laryngeal aspiration? Such technologies would greatly advance research and benefit clinical practice.
3. Do exogenous stimuli guide (or mislead) development of feeding and airway protective reflexes in preterm infants? For example, does prolonged intubation and artificial ventilation perturb the development of sensory and motor systems that underlie airway protection, leading to difficulties after the infant is extubated?
4. How does infection/inflammation alter control of feeding and airway protection?
5. What is the role of repeated laryngeal penetration of oral or regurgitated gastric contents in the pathophysiology of central/obstructive apneas, hypoxemia, bradycardia, or chronic pulmonary disease in preterm infants?

EVALUATION OF THE UPPER AIRWAY USING IMAGING AND OTHER TECHNIQUES

Background

As previously noted, the upper airway serves multiple functions, including respiration, swallowing, and speech. To accommodate these functions, the upper airway size and

shape can be actively modulated neuronally, whereas at other times it is passively collapsible. During development, the upper airway undergoes significant structural and functional changes that affect its size, shape, and mechanical properties (50). Another important characteristic of the upper airway is that it is a virtual conduit. Its anatomical boundaries are defined by other tissues that determine its properties at each moment.

Abnormalities of the upper airway require prompt attention, since these often alter ventilatory patterns and gas exchange, particularly during sleep, when upper airway motor tone and ventilatory drive are diminished. Polysomnography is used as a standard tool to establish the existence and severity of such disorders during sleep (51). However, understanding the pathophysiology and mechanisms leading to upper airway disorders requires additional diagnostic tools.

One of the most important respiratory disorders in childhood is the obstructive sleep apnea syndrome (OSAS) (52). Other important upper airway disorders in childhood that may not necessarily lead to OSAS include congenital malformations, dynamic dysfunction, compression of the airway, swallowing dysfunction, and acquired deformities due to infection, systemic diseases, or trauma.

The preferred radiological or visual technique to evaluate the upper airway in children with structural or functional abnormalities is determined by the clinical condition of the patient, severity and complexity of the disorder, the diagnostic expertise of team, and the resources available. A common technique in clinical practice is upper airway endoscopy that is used to evaluate both the anatomy and function of the airway, and is commonly performed under sedation or anesthesia. Radiological measures such as neck radiographs and cephalometry provide a static two-dimensional assessment of the airway (53). Fluoroscopy provides a functional evaluation of airway dynamics, but involves ionizing radiation. Upper airway acoustic reflection provides limited information about the shape of the airway (54), but its use has not been standardized in children. Ultrasound is an important diagnostic radiological technique that currently has limited application for imaging the upper airway due to poor transducer-air coupling (55). A promising technique allowing quantitative imaging of upper airway anatomy and motion is real-time endoscopic optical coherence tomography. This modality uses broadband, low-coherent light combined with interferometry to produce high-resolution images analogous to B-mode ultrasonography. The use of this technique has recently emerged as an investigational tool to study the airways of both adults and children (56–59).

The most advanced imaging techniques to evaluate upper airway characteristics are computed tomography (CT) and magnetic resonance imaging (MRI) (60, 61). Both provide a three-dimensional evaluation of the airway and surrounding tissues with very high precision. CT technology is hampered by its use of ionizing radiation, though cone-beam CT scans may reduce the radiation dose significantly, and may be useful for imaging the airway in children in the future. Other limitations of CT and MRI include motion artifact due to tidal breathing or active airway obstruction, the need for sedation in infants and young children to prevent motion artifact, and cost. Dynamic respiration-gated techniques with CT and MRI have been recently introduced by several groups to study airway dynamics, and may provide functional data based on measures of collapsibility (62, 63). The utility of such imaging techniques, along with computation models of upper airway fluid and tissue mechanics are beginning to provide better understanding of the complex anatomical and functional interactions leading to OSAS and other respiratory disorders in both children and adults. In the future, improved diagnostic methods based on

computed models derived from imaging may lead to better approaches for surgical correction where appropriate (64).

PRIORITY AREA 1: Determine the Developmental Changes in Upper Airway Anatomy and Function during Childhood (from the Neonatal Stage through Puberty), Across Sexes and Ethnicities

Despite the technical advancements in the past several years in upper airway image acquisition with new techniques such as CT, MRI, and optical coherence tomography, the role of these techniques as clinical tools for predicting OSAS or risk of OSAS is limited. It should be emphasized that normative values of upper airway structure and function during development are lacking at this time. Similarly, protocols for these newer techniques are not standardized, and are performed under different levels of upper airway activation and various sedation and anesthetic protocols. In addition, it is not known how these conditions correlate to sleep state. Real-time imaging of the airway during natural sleep in healthy children using the above methodologies has not been performed so far and is a major technical undertaking.

Research opportunities/questions

1. Apply accurate, efficient, and standardized imaging modalities to determine developmental changes in upper airway anatomy and function during childhood. Optimal methods should provide 2D and 3D static and dynamic measures of the upper airway. Methods should be safe and should limit the use of ionizing radiation and sedation, and be used with standardized data acquisition and analysis protocols. Promising imaging modalities include but are not limited to endoscopy, pharyngometry, cone-beam CT, optical coherence tomography, ultrasound, functional MRI, MR spectroscopy, and MR elastography.
2. Determine the effects of neuronal activation on upper airway size and function in children during wakefulness and different stages of sleep, and the influence thereon of sedatives and anesthesia.
3. Develop low-cost, readily available techniques for evaluating upper airway structure and/or function in children.

PRIORITY AREA 2: Apply Imaging Modalities or Other Techniques to Determine the Sites of Obstruction and the Pathophysiological Mechanisms that Lead to or Predict Morbidity in Children with Altered Upper Airway Anatomy and/or Function, such as Adenotonsillar Hypertrophy, Congenital Upper Airway Malformations, Acquired Upper Airway Abnormalities, Obesity, and Neurological Disorders

Research opportunities/questions

1. Apply accurate, efficient, and standardized imaging modalities, as in Priority Area #1, to the understanding of upper airway anatomy and function in children with the above upper airway malformations and diseases.

PRIORITY AREA 3: Apply Advanced Dynamic Imaging Modalities to Study Upper Airway Mechanics

Research opportunities/questions

1. Study upper airway mechanics in congenital conditions associated with dynamic collapse of the upper airway such as laryngomalacia and tracheomalacia.
2. Study upper airway mechanics in acquired conditions with flow limitation and airway obstruction to determine re-

gional tissue motion during sleep. This would provide novel information about the mechanisms of airway collapse and stability, and how this changes with age.

3. Develop reliable numerical tools for modeling airflow and pressure through a deformable airway.

PRIORITY AREA 4: Apply Imaging Techniques to Determine the Surgical and Other Interventional Outcomes Impacting Upper Airway Structure and Function (Ventilation, Swallowing, and Speech) in Children with Congenital and Acquired Upper Airway Malformations and Craniofacial Disorders Affecting their Nasal, Pharyngeal, Hypopharyngeal, and Laryngeal Airways

Research opportunities/questions

1. Develop validated optimal interventional planning tools based on simulation and computed mechanical models of the upper airway for children with upper airway disorders requiring interventional procedures.
2. Specifically, use imaging techniques along with functional techniques (e.g., polysomnography) to study the surgical outcomes for palatoplasty, pharyngeal flap, adenotonsillectomy, tonsillectomy, laryngotracheal reconstruction, and craniofacial surgeries such as mandibular and maxillary advancement.

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