National Sleep Disorders Research Plan

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SECTION 5 - SLEEP DISORDERS

SLEEP-DISORDERED BREATHING

Adult

Background

Sleep-Disordered breathing (SDB) describes a group of disorders characterized by abnormalities of respiratory pattern (pauses in breathing) or the quantity of ventilation during sleep. Obstructive sleep apnea (OSA), the most common such disorder, is characterized by the repetitive collapse or partial collapse of the pharyngeal airway during sleep and the need to arouse to resume ventilation. Sleep is thus disrupted, yielding waking somnolence and diminished neurocognitive performance. The recurrent sleep arousal in association with intermittent hypoxia and hypercapnia has been implicated in the occurrence of adverse cardiovascular outcomes. In addition, there is evolving evidence that SDB may contribute to insulin resistance and other components of the metabolic syndrome. Despite considerable progress, most patients remain undiagnosed and the principal therapeutic approach, continuous positive airway pressure (CPAP), remains somewhat cumbersome and hence not associated with optimal compliance rates.

SDB is exacerbated by alcohol intake. We continue to have a very incomplete understanding of the neurobiologic mechanisms responsible for the sleep-induced changes in upper airway motor control that lead to pharyngeal collapse. The reversibility with therapy of apnea-induced hypertension and other presumed adverse cardiovascular outcomes is largely untested. The explanation for reduced prevalence of SDB in women compared to men and why women present for therapy even less often than the prevalence numbers would suggest remain unresolved. It is unclear to what extent SDB in the elderly represents the same disorder as is encountered in younger populations and thus deserves similar therapy.

Cheyne-Stokes respiration, another type of SDB, is characterized by a crescendo - decrescendo pattern of respiration and is commonly seen during sleep in patients with congestive heart failure. The presence of this

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respiratory pattern appears to be an important risk factor for the progression of heart failure. More data are needed, however, to clarify the mechanisms leading to Cheyne-Stokes respiration, the impact of this abnormal ventilatory pattern on cardiac function, and the effect of treatment on survival.

Progress In The Last 5 Years

- Reversibility with CPAP therapy of many of the neurocognitive and quality of life detriments associated with SDB is suggested by relatively small, short-term trials.

- The strength of the association between SDB and systemic hypertension in animal models and large, prospective epidemiologic studies is becoming more evident. Cross-sectional data also suggest an important association between SDB and stroke, myocardial infarction, and congestive heart failure.

- Studies addressing control of the pharyngeal musculature awake and asleep have demonstrated the ability of these muscles to respond to local stimuli awake, thereby compensating for deficient anatomy/collapsibility and maintaining airway patency. The loss of these reflex mechanisms during sleep is an important factor in the pathogenesis of SDB.

- Increasing evidence suggests a familial/genetic influence on predisposition to SDB independent of obesity. This genetic influence may be mediated differently in different racial and ethnic groups (Section IV).

- The efficacy of oral appliances (primarily mandibular advancing devices) in patients with mild to moderate SDB and of upper airway surgical procedures over a range of apnea severity has been evaluated. However, more information is needed before their roles can be clearly delineated.

- Data suggest that positive airway pressure therapy can, over several weeks, eliminate Cheyne-Stokes respiration in heart failure patients and lead to improved transplant-free survival.

Research Recommendations

- Investigate and advance our understanding of the genetic, neurobiologic and physiologic mechanisms that are pathophysiologically important in the development, potentiation, and maintenance of SDB. Studies are also needed to access the interaction between cardiac dysfunction and the ventilatory control system in the pathogenesis of Cheyne-Stokes respiration.

- Conduct adequately powered clinical trails, particularly in high risk populations, to assess the impact of therapy of SDB on functional status, psychiatric disorders, neurocognitive function, and other disease processes (hypertension, cardiovascular disease, metabolic syndromes, etc). Studies assessing the impact of successful therapy of Cheyne-Stokes respiration on cardiac dysfunction, quality of life and survival are needed as well.

- Design new and improved modalities for the treatment of SDB, including pharmacologic, surgical, oral appliance, behavioral, muscle stimulation, positive airway pressure (including CPAP compliance), and other novel approaches. Methods to individualize these therapies to the different SDB phenotypes are also needed, for example improved upper airway imaging approaches to define site of collapse.

- Develop novel non-invasive screening / diagnostic methodologies that are less expensive and more widely applicable than standard full polysomnography. This might include biomarkers as indicators of the presence of SDB, of its severity or of its consequences.

Pediatric

Background

Snoring, a symptom of increased upper airway resistance during sleep, is extremely frequent in children, and affects 18-20% of infants, 7-13% of 2-8 year-old children, and 3-5% of older children. The pathophysiology of SDB in children is still poorly understood. Indeed, while adenotonsillar hypertrophy is certainly a major contributor to SDB, other factors such as obesity, craniofacial genetics, and neural control mechanisms of upper airway patency also appear to be important. It is clear that the spectrum of disease and morbidity associated with SDB in children is expanding. As such, degrees of severity that might have once been considered clinically irrelevant are now recognized as having substantial neurobehavioral and cardiovascular consequences.

Progress In The Last 5 Years

- In recent years, it has become apparent that SDB and snoring are not as innocuous as previously thought. Indeed, epidemiological and pre-post treatment analyses have identified substantial morbidities that primarily affect cardiovascular and neurobehavioral systems. These morbidities include pulmonary hypertension, arterial hypertension, nocturnal enuresis, reduced somatic growth, learning and cognitive deficits, and behavioral problems that resemble attention deficit-hyperactivity disorder.

- Failure to timely diagnosis and treat may prevent some of these morbid complications from being completely reversible, leading to long-lasting residual consequences. However, the point of transition between what constitutes pathology and what is normal remains to be defined.

- Improved phenotypic characterization of SDB and its manifestations are facilitating extrapolation of basic science concepts to the pediatric population. Extended population studies are needed which incorporate gene databases and also include multi-organ multi-functional categorization of SDB-related morbidity and response to therapy. Such studies would allow for development of databases permitting correlation analyses of large datasets and exploration of multiple hypotheses generated from basic research findings.

- As part of such phenotype delineation, development of more sensitive and accurate tools for definition of disease and morbidity are needed. Currently available tools are insensitive to morbidity and do not provide accurate determinations of the degree of homeostatic disturbance that occurs during sleep and during daytime.

Research Recommendations

- Develop longitudinal normative data on sleep and cardiorespiratory patterning in children.

- Identify genes and gene products that may contribute to the pathophysiology of SDB. Conducting these studies in pediatric populations may have distinct advantages because they are less likely to be "contaminated" by age-associated co-morbidities present in adult populations. Some of the "at-risk genes" may be operative only during infancy and childhood, e.g., genes responsible for immune modulation and lymphatic tissue growth, while other genes such as those underlying obesity or craniofacial phenotype, appear applicable to both children and adults. In addition, environmental factors or gene-gene interactions during childhood may modify the phenotypic expression of the disease during adulthood.

- There is considerable variation in the magnitude of SDB associated morbidities in both children and adults, and this heterogeneity in end-organ injury could be due to differences in gene and protein responses to the various components of SDB. Identification of such genes/proteins, their functions and interactions, and their post-translational modifications using currently available genomic and proteomic approaches may provide opportunities for development of promising targets for intervention and for reducing morbidity.

- Longitudinal studies are needed to assess the long-term impact of SDB during childhood and into adulthood. Particular attention to outcomes among obese children is important considering the increasing prevalence of obesity in children.

- One of the major limitations in diagnosing SDB is the need for relatively complex, burdensome, and costly procedures such as overnight polysomnography. Research efforts need to focus on development of reliable screening methods that are applicable to children and to provide accurate indicators of either the presence/absence of the disease or the occurrence of end-organ morbidity. Such developments include, for example, application of new biomedical sensor technologies, multi-modality imaging strategies, development of disease-related artificial intelligence networks, and systematic exploration of gene and protein markers in biological fluids.

- First-line treatment of pediatric SDB routinely relies on surgical removal of the tonsils and adenoids. However, this treatment does have measurable morbidity, mortality, and financial cost. Thus, novel interventional approaches need to be developed.


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