A model-based approach to phenotyping sleep-related breathing disorders in pediatric obesity

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Abstract— The prevalence of overweight and obesity in children has increased dramatically over the past two decades. A significant fraction of these obese children also have sleep-related breathing disorders. The ongoing study described in this talk combines overnight physiological measurements with a minimal closed-loop computational model of ventilatory control to investigate why this subject population exhibits large variations in sleep and clinical characteristics. The knowledge derived from this study may lead to a better understanding of the mechanisms through which the different phenotypes of sleep-related breathing disorders (SRBD) occur in obese children, and could be useful in providing better guidelines for customizing therapeutic strategies to individual patients.

Obstructive sleep apnea (OSA) has been reported to occur at prevalence rates on the order of 50% in morbidly obese children, compared to only a few percent of the general pediatric population. This marked difference in prevalence rates becomes even larger if one were to include other forms of sleep-related breathing disorders (SRBD), such as hypoventilation and hypercapnia or hypoxemia without frank obstructions. Although 45% of obese children have adenotonsillar hypertrophy, adenotonsillectomy eliminates OSA in less than half of the obese subjects who elect to undergo this form of treatment. These data along with other recent findings suggest that, although upper airway anatomy is a key mediator in OSA, other factors that affect dynamic changes in upper airway patency, such as chemoreflex control and state dependence, also play important roles. Moreover, the pool of subjects with obesity-related SRDB display a large variation of polysomnographic and clinical characteristics. These may be classified broadly into the following 4 phenotypic categories: (a) primary snorers with no abnormalities of gas exchange, respiratory pattern or sleep disruption; (b) obstructive hypoventilation with hypercapnia or hypoxemia with near-normal respiratory or sleep patterns; (c) high arousal frequency without prominent gas exchange abnormality, obstructive apneas or hypopneas (includes upper airway resistance syndrome); (d) traditional OSA with recurrent episodes of obstructive hypopnea and apnea. We hypothesize that this diversity in phenotypic behavior results from the existence of different underlying physiological mechanisms, and that a quantitative dynamic model would allow us to better delineate the mechanistic differences.

In this talk, we describe the application of an approach in which we employ a minimal closed-loop model to estimate the key parameters that influence ventilatory stability in subjects during sleep. These parameters include: (a) “dynamic chemoresponsiveness” – the transfer function relating changes in alveolar \( P_{CO_2} \) to changes in ventilator drive; (b) the lung-to-chemoreceptor circulatory delay; (c) “plant dynamics” – the transfer function relating ventilation to alveolar \( P_{CO_2} \); (d) the arousal threshold; (e) the arousal drive; and (f) the upper airway closing pressure (\( P_{crit} \)).

Subjects from the 4 phenotypic categories are studied during an overnight session in which polysomnographic variables are recorded and the following experimental interventions are applied: (1) Baseline (no intervention): continuous positive airway pressure (CPAP) is set at the minimal level (-3 cmH\(_2\)O) to overcome the breathing circuit resistance. Assuming a single compartment model of gas exchange in the lungs, the plant dynamics transfer function is estimated by assuming changes in ventilation to be the input and end-tidal \( P_{CO_2} \) to be the output; (2) Determination of ventilatory response to ventilator-induced sighs: subject breathes at the therapeutic CPAP level. Inspiratory pressure is abruptly increased by 5 cmH\(_2\)O for 2-3 breaths and then returned to therapeutic CPAP level. The “loop transfer function” is estimated by autoregressing breath-by-breath ventilation on its past values, using a method similar to that employed by Asyali et al.[1]; (3) Determination of \( P_{crit} \): starting at the therapeutic level, CPAP is reduced slowly to a minimal pressure of 3 cmH\(_2\)O in 4 to 5 equal 10-breath steps. Breaths with flow limitation are selected, the median airflow and mask pressure at each CPAP level are fitted by linear regression, and \( P_{crit} \) is taken to be the value at which there is no airflow; (4) Determination of arousal threshold and arousal drive: while the subject breathes at the therapeutic CPAP level, an inflatable balloon valve is activated at the end of expiration to occlude airflow into or out of the facemask until completion of the first post-arousal breath. Mask pressure immediately before arousal gives an estimate of the arousal threshold, whereas the change in mask pressure immediately following arousal is taken to represent arousal drive.

The estimated parameters are used in a computational model that simulates ventilatory control dynamics during sleep. Metrics derived from these simulations are compared against the corresponding indices derived from the observed characteristics of SRBD in the 4 phenotypic categories.

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