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Model-Based Studies of Autonomic and Metabolic Dysfunction in Sleep Apnea

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Abstract Obesity and insulin resistance are highly prevalent in subjects diagnosed with sleep apnea. One factor common to obesity, sleep and insulin resistance is autonomic nervous system dysfunction, in particular, sympathetic overactivity. Although the causal links among these factors are not well understood, it is likely that the vicious cycle of interplay among these factors predisposes to the emergence of "metabolic syndrome", a convergence of obesity, hypertension, insulin resistance and dyslipidemia that is appearing in epidemic proportions in the United States and other countries. This chapter provides an overview of the ongoing experimental and modeling studies in my laboratory aimed at elucidating and quantifying the relationships among autonomic dysfunction, insulin resistance and severity of sleep apnea in overweight subjects. These studies employ a "minimal modeling" approach to extract information characterizing autonomic function from noninvasive cardiorespiratory measurements. We subsequently determine the relationship of these model parameters to the parameters estimated from the Bergman minimal insulin-glucose model using data obtained from the frequently sampled intravenous glucose tolerance test performed on the same individuals.

1 Introduction and Background

The current evidence suggests that diet, physical activity, glucose-insulin control, and the insulin-mediated regulation of sympathetic nervous system (SNS) activity are tied together in a delicate balance that, if disrupted, can lead to obesity and obesity-related disorders. Such obesity-related disorders include Type 2 diabetes, hypertension, and the combination of autonomic and metabolic dysfunction now commonly referred to as "metabolic syndrome". There is also growing recognition that the added factors of sleep-disordered breathing (SDB) and other forms of sleep disruption can contribute significantly to autonomic imbalance and insulin resistance (Coughlin et al. 2004). Chronic sleep deprivation resulting from SDB or behavioral causes can lead to excessive daytime sleepiness and lethargy, which in turn can contribute to increasing obesity (Tasali and Van Cauter 2002). It is now also well known that SDB is associated with sympathetic overactivity (Fletcher 2003). Since obesity

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is highly prevalent in subjects with SDB, it has been suggested that the presence of occult SDB might be an additional factor that can contribute to the elevated sympathetic traffic associated with obesity (Somers 1999). On the other hand, there is also recent evidence that indicates that SDB is likely not the sole cause of SNS overactivity in human obesity (Esler and Eikelis 2006). Recent studies have found a positive correlation between SDB and increased insulin resistance (Punjabi and Polotsky 2005), raising the question of whether a significant part of the correlation between obesity and insulin resistance can be accounted for by the presence of occult SDB. Indeed, it has been shown recently that treatment of SDB with continuous positive airway pressure (CPAP) reduces insulin resistance after 3 months of home therapy, independent of any changes in body mass index (Harsch et al. 2004).

Theoretically, SDB could lead to insulin resistance through at least two mechanisms. It is well established that SDB produces SNS overactivity; the latter leads to increased catecholamine release, which produces hyperglycemia and, in turn, hyperinsulinemia, which promotes insulin resistance (Chasens et al. 2003). Chronic exposure to the intermittent hypoxia resulting from SDB may also contribute directly to insulin resistance. Since hyperinsulinemia stimulates SNS activity, a vicious cycle could well develop that leads to worsening autonomic function and insulin resistance. Along with genetic factors and other potential complications arising from obesity, these conditions provide an ideal backdrop in which diabetes and hypertension can develop.

Spectral analysis of heart rate variability (HRV) has been used extensively as a noninvasive means of assessing autonomic function (Task Force 1996). However, there are important limitations that are often overlooked. For instance, power in the high-frequency band (0.15–0.4 Hz) is highly sensitive to differences or changes in ventilatory pattern (Brown et al. 1993). This caveat is particularly important when spectral analysis of HRV is performed in subjects under various conditions with irregular or periodic forms of ventilation (Khoo et al. 1999). The low-frequency power or the ratio of low-frequency to high-frequency power (LHR) are frequently cited as measures of SNS activity, but it is now fairly well established that these indices contain a substantial parasympathetic contribution (Task Force 1996). Also, there is no significant correlation between low-frequency power or LHR and baseline peroneal sympathetic nerve activity (Eckberg 1997).

The limitations inherent in using HRV or blood pressure variability to infer autonomic function can be circumvented to some extent by focusing not on the oscillations themselves but on how they are correlated with each other (Baselli et al. 1988). Over the past several years, we have developed a minimal closed-loop model that explicity incorporates the very significant effects of respiration on heart rate and blood pressure, and consideration of feedback effect of blood pressure on heart rate and vice versa (Belozeroff et al. 2002). We have applied this model to assess autonomic cardiovascular control in SDB in various subjects groups and conditions (Belozeroff et al. 2003; Jo et al. 2003; Chaicharn et al. 2009). The model we have introduced enables the characterization of the dynamic interrelationships between various pairings of the key variables: respiration, R-R interval (RRI) and systolic blood pressure (SBP). The techniques of system identification are then applied to estimate the gains and temporal characteristics of the "black boxes" that represent these interrela-

tionships. In the model, fluctuations in RRI stem from direct respiratory-cardiac coupling ("RCC") and/or blood pressure fluctuations via the baroreflex ("ABR"). Because of the closed-loop nature of the problem, the equations that characterize the model have to be solved in the time domain, since they require the imposition of causality constraints to delineate the feedback from feedforward portions of the closed-loop structure (Khoo 2000). Based on our accumulated experience from previous studies with this model, RCC gain provides a good index of vagal modulation of heart rate, whereas ABR gain, which reflects baroreflex sensitivity, appears to be influenced by both vagal and sympathetic tone.

2 Methods and Data Analysis

Because of the close connections between metabolic and autonomic factors, we are conducting studies in which multiple measurements reflecting autonomic activity, metabolic function and SDB status are made in the same group of subjects. We know of no existing studies that have adopted this multi-faceted approach to the problem. As well, to minimize the potential confounding effects of duration of exposure to SDB or insulin resistance, we have chosen to focus on overweight pediatric subjects. The study design consists of the following steps:

A. Recruitment of overweight (body mass index greater than 85th percentile for age and sex, according to CDC percentile charts) children, 10–17 years of age, from the pool of outpatients referred for overnight polysomnography. Exclusion criteria include history of cardiac disease, chronic lung disease, renal disease, diabetes, craniofacial malformations, pulmonary hypertension, or systemic hypertension.

B. Each of the recruited subjects is required to complete the following protocol: (1) overnight polysomnography; (2) measurements of awake spontaneous respiration, heart rate and continuous blood pressure in the supine and standing postures (3) dual energy x-ray absorptiometry (DEXA) scan to determine body composition; (4) the insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT) (Bergman et al. 1985), following overnight fast. The requirement for overnight fasting prior to the FSIVGTT, the invasiveness of the FSIVGTT, and the need to perform the autonomic measurements under relatively relaxed conditions, mean that the metabolic and autonomic tests have to be conducted on different days.

Using our minimal closed-loop model of cardiorespiratory control, the dynamic gains of ABR and RCC components are estimated from the measurements of resting respiration, RRI and SBP. The Bergman minimal model (Bergman et al. 1985) is used to quantify the in vivo kinetics of glucose and insulin from the FSIVGTT. Specifically, the model produces estimates of peripheral insulin sensitivity (SI) and the acute insulin response to glucose (AIRg), an index of pancreatic beta-cell response. The product of SI and AIRg yields the disposition index, an integrated measure of pancreatic beta-cell function. From the DEXA scan, we obtain estimates of adiposity in terms of percent body fat. The polysomnogram from each subject produces values of apnea-hypopnea index (AHI), arousal index and desaturation index, along with sleep architecture information.

3 Preliminary Results

Based on our preliminary analysis of data from 14 subjects (age = 13.2 ± 1.9 yrs, BMI= 35.5 ± 7.2, we have found log(SI) to be negatively correlated with log(desaturation index) ($r = -0.60$, $P = 0.024$). However, SI is not correlated with AHI or arousal index. The correlation between SI and desaturation index remains significant even after adjusting for adiposity. ABR gain is not correlated with SI; instead, it is correlated with disposition index ($r = 0.88$, $P < 0.001$). RCC gain is negatively correlated with fasting glucose level. On the other hand, the impact of the SDB indices on the autonomic parameters is smaller than expected: RCC gain is found to decrease with arousal index ($r = -0.67$, $P = 0.035$), but there are no other correlations between the autonomic parameters and SDB indices. This is likely due to the fact that the severity of SDB in the subjects studied so far is in the mild-to-moderate range ($1.0 \leq \text{AHI} \leq 14.1\ \text{h}^{-1}$).

4 Conclusions

A limitation of this study is that is cross-sectional in nature and it is based on noninvasive data obtained in humans, which makes it difficult to arrive at definitive conclusions about causality. Nevertheless, our findings to date suggest that the development of insulin resistance is enhanced in obese adolescents by sleep-disordered breathing primarily through chronic exposure to intermittent hypoxia. In the group of subjects studied, who have mild-to-moderate SDB, autonomic function is affected by SDB primarily through exposure to the sleep disruption produced by the repetitive arousals, and not as much by the accompanying intermittent hypoxia. Thus, autonomic dysfunction appears to be unnecessary as an intermediate step linking SDB to insulin resistance. Instead, our preliminary results suggest that the intermittent hypoxia of SDB can lead directly to insulin resistance, and that the ensuing metabolic dysfunction and SDB-related sleep fragmentation are both important drivers of the development of autonomic dysfunction.

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