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Sleep-related Changes in Autonomic Control in Obstructive Sleep Apnea: A model-based perspective

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Abstract

This paper reviews our current understanding of the long-term effects of obstructive sleep apnea (OSA) on cardiovascular autonomic function in humans, focusing directly on the knowledge derived from noninvasive measurements of heart rate, beat-to-beat blood pressure (BP), and respiration during wakefulness and sleep. While heart rate variability (HRV) as a means of autonomic assessment has become ubiquitous, there are serious limitations with the conventional time-domain and spectral methods of analysis. These shortcomings can be overcome with the application of a multivariate mathematical model that incorporates BP, respiration and other external factors as physiological sources of HRV. Using this approach, we have found that: (a) both respiratory-cardiac coupling and baroreflex dynamics are impaired in OSA; (b) continuous positive airway pressure therapy partially restores autonomic function; (c) baroreflex gain, which increases during sleep in normals, remains unchanged or decreases in OSA subjects; and (d) the autonomic changes that accompany transient arousal from NREM sleep in normals are largely absent in patients with OSA.

1. Introduction

It has long been known that, in healthy subjects, sleep onset leads to a lowering of respiration, heart rate, blood pressure, cardiac output and systemic vascular resistance; by and large, these physiological variables continue to decrease as sleep progresses from the lighter to deeper stages of non-rapid eye movement (non-REM) sleep (Bristow et al. 1969; Mancina and Zanchetti, 1980; George and Kryger, 1985; Phillipson and Bowes, 1987). Respiratory sinus arrhythmia (RSA) and total heart rate variability are increased in stages 1 and 2 sleep relative to wakefulness, but become reduced in the deeper stages of non-REM sleep (Zemaityte et al., 1984; Lombardi and Parati, 2000). In REM sleep, mean heart rate is lower compared to wakefulness but higher relative to slow-wave sleep (Zemaityte et al., 1984; Cajochen et al., 1994).

The key features that distinguish subjects with obstructive sleep apnea (OSA) from normal controls are the net increase in mean systemic blood pressure and the large periodic

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variations in heart rate and blood pressure that accompany each apnea-arousal cycle (Guilleminault et al., 1984; Parish and Shepard, 1990; Leung and Bradley, 2001). The surge in blood pressure towards apnea termination is believed to be mediated by increased sympathetic activity resulting from the episodic hypoxemia (Leuenberger et al., 1995; Somers et al., 1995). Transient arousal from sleep, which almost invariably accompanies the termination of upper airway obstruction, also leads to surges in arterial blood pressure and increased sympathetic activity (Ringler et al., 1990; Morgan et al., 1996). It is reasonable to expect the repeated exposure to the intermittent hypoxia, sleep fragmentation and fluctuations in autonomic activity that accompany OSA to lead to adverse effects in the long term. This is the basic premise underlying many studies that have sought to establish the causal links between OSA and cardiovascular disease (Somers et al., 2008). Moreover, although many mechanisms, such as endothelial dysfunction or inflammation, have been proposed as potential causal factors, abnormal autonomic control is generally accepted to play an important role (Leung, 2009). The main purpose of this paper is to review our current understanding of the long-term effects of OSA on autonomic function, with special attention paid to what has been learnt from noninvasive measurements of heart rate variability and blood pressure variability during sleep. The material presented in this review is not intended to be comprehensive or complete. Instead, this paper offers an additional perspective that is derived from the application of dynamic systems analysis to the problem at hand. For more comprehensive coverage, the reader is referred to several existing outstanding reviews of the subject matter (Caples et al., 2007; Somers et al., 2008; Leung, 2009; Dempsey et al., 2010; Lurie, 2011).

2. Chronic effects of OSA on sympathetic activity

Sympathetic tone during both sleep and wakefulness has been found to be significantly elevated in patients with OSA relative to normal controls, based on studies using peroneal microneurography (Somers et al., 1995), plasma catecholamines (Carlson et al., 1993) or urinary catecholamines (Dimsdale et al., 1995). Treatment with continuous positive airway pressure (CPAP) over a duration of between 1 and 2 years reduced daytime plasma norepinephrine by roughly 50% in a group of patients with severe OSA (Hedner et al., 1995). Daytime muscle sympathetic nerve activity (MSNA) in OSA subjects was also found to be reduced following CPAP therapy over a 2-year duration (Imadojemu et al., 2007). These chronic autonomic abnormalities suggest the existence of a mechanism that allows the acute effects of the intermittent hypoxia or arousal that accompany OSA cycle to be carried over into the daytime. But which of these factors exerts a greater cumulative impact on the autonomic nervous system?

In prospective animal studies, the answer appears to be intermittent hypoxia. In the study of Brooks et al. (1997), daytime hypertension was produced in dogs that were exposed to artificially-induced periodic airway obstructions for several weeks; however, sustained exposure to periodic acoustically-induced arousals without prior upper airway obstruction led only to nocturnal hypertension with no carry-over effect in the daytime. In a rat model, sustained hypertension developed after a few weeks of exposure to intermittent hypoxia without any accompanying upper airway obstruction or artificially induced arousals (Fletcher et al., 1992). In humans, the relative importance of intermittent hypoxia vis-à-vis arousal is not as clear. In two studies on normal young adults (Xie et al., 2000; Cutler et al., 2004), exposure to intermittent asphyxia over a period of 20 min led to sympathetic activation that persisted following removal of the stimulus. The results were similar regardless of whether these exposures occurred against a background of hypercapnia or isocapnia, confirming that the primary mediator for the increase in sympathetic activity was the intermittent hypoxia. Two other studies (Leuenberger et al., 2005; Leuenberger et al., 2007) have also demonstrated sustained substantial increases in muscle sympathetic nerve

activity in healthy subjects following exposure to repetitive hypoxic apneas for a total duration of 30 mins. On the other hand, in a retrospective study (Loredo et al., 1999) relating daytime plasma and urine norepinephrine levels to polysomnographic measures of OSA severity, the measures of daytime sympathetic activity were correlated only with movement arousals. In another study (Norman et al., 2006), 24-hour ambulatory blood pressure was monitored in 46 subjects with moderate-to-severe OSA before and after 2 weeks of either CPAP therapy or sham-CPAP with supplemental nocturnal oxygen. Following the treatment period, subjects treated with CPAP showed a significant reduction in daytime and nighttime blood pressures, whereas no changes were found in those subjects treated with sham-CPAP and supplemental nocturnal oxygen. This result suggests that elimination of intermittent hypoxia during the night had less of an impact in improving cardiovascular autonomic control than CPAP therapy, which eliminated both the intermittent hypoxia and arousals. Thus, the relative importance of repetitive arousal towards long-term impairment of the autonomic nervous system appears to be substantially higher in humans than in animal models of OSA.

3. Chronic effects of OSA on heart rate variability

Autonomic nervous system activity in OSA subjects has also been assessed through more indirect methods such as heart rate variability (HRV). The advantage of HRV monitoring lies in the ease, noninvasiveness and non-intrusiveness of obtaining the measurements on a continuous basis over significant lengths of time, including during sleep, since subject cooperation is not necessary. It is commonly accepted that only parasympathetic (vagal) activity accounts for the contribution to the high-frequency (HF, 0.15–0.4 Hz) component of HRV (ESC/NASPE Task Force 1996). On the other hand, the low-frequency (LF, 0.04–0.15 Hz) component of HRV can be due to both vagal and sympathetic activities (Eckberg 1997). The ratio between LF and HF spectral powers has been used by researchers broadly as an index of ‘sympathovagal balance’ (Malliani et al., 1991).

Previous studies employing spectral analysis of HRV have generally reported significantly reduced HF power and elevated LF/HF ratios in awake OSA subjects relative to normal controls (Narkiewicz et al., 1998; Wiklund et al., 2000). Similar findings on frequency-domain indices of HRV have appeared in studies of subjects with OSA conducted during sleep (Shiomi et al., 1996; Vanninen et al., 1996) or through Holter monitoring over 24 h (Aydin et al., 2004; Gula et al., 2003). By and large, these findings support the notion that sympathetic modulation of HRV is higher and parasympathetic activity is reduced in OSA. However, in OSA patients during sleep, the respiratory modulation of heart rate is not confined to within-breath changes (ie. respiratory sinus arrhythmia as generally observed in wakefulness) but also takes the form of large cyclical variations that correlate with the episodic apneas or hypopneas (Guilleminault et al., 1984; Khoo et al., 1999). Although these large cyclical variations in heart rate generally fall into the very low frequency band (<0.04 Hz), LF and HF power of HRV have also been found to increase during OSA episodes (Keyl et al., 1996). In the study of Guilleminault et al. (1984), administration of atropine sulfate eliminated these very low frequency (VLF) oscillations in heart rate, even though the pharmacological intervention had no effect on type or duration of apnea or sleep staging. These observations suggest that: (1) the VLF component of HRV in OSA results from the same coupling mechanism between respiration and heart rate that generates respiratory sinus arrhythmia, except that in this case, the coupling occurs at periodicities consistent with OSA cycling; and (2) respiratory-cardiac coupling in the VLF and HF bands is mediated primarily by the parasympathetic branch of the autonomic nervous system. Thus, as proposed by Saul et al. (1998), respiratory modulation of heart rate takes place over a range of frequencies much broader than the HF band that is associated with RSA during wakefulness.

4. Confounding effects of respiration on heart rate variability

The premise that RSA magnitude is directly and proportionally related to cardiac vagal tone has been based primarily on experiments in animals or humans in which pharmacological interventions were employed to vary autonomic activity (Katona and Jih, 1975; Berntson et al., 1997). In these studies, respiration was either controlled or spontaneous and little changed while vagal activity was altered. However, the natural variability in respiration during sleep in both normals and OSA patients can seriously confound this simple relationship. Hypopnea, for instance, will increase arterial P_{CO_2} and lower arterial P_{O_2} levels, in turn, activating the chemoreceptors, which then act to increase ventilatory drive and alter autonomic input to the heart. On the other hand, the consequent increase in breathing increases vagal feedback from the lungs, and this has been shown to exert an inhibitory influence on sympathetic activity.

To circumvent this problem, we have proposed an algorithm (Khoo et al., 1999) that computationally adjusts the estimated HRV spectral indices for differences in ventilation and ventilatory pattern during sleep. The basic notion is to partition the heart rate time-series into a component that is correlated with respiration and a respiration-independent component. From the respiration-correlated component, the transfer function between respiration and heart rate is estimated. This transfer function is next used to predict what the respiration-correlated component of HRV would be if the respiration time series during that interval of time were to take the same form as a “baseline” respiration time-series measured during a short period of quiet wakefulness immediately prior to the start of the sleep study. Finally, the predicted respiration-correlated component is added to the respiration-uncorrelated component to generate the “respiration-adjusted” heart rate time-series, from which the respiration-adjusted LF and HF power (Wang et al., 2008). This “compare apples to apples” approach is analogous to the standard practice of adjusting for confounding factors in statistical analysis.

5. Multivariate modeling approach: the minimal model

An alternative approach is to more explicitly model the dependencies among the key measurable variables involved in cardiovascular autonomic control. Here, we turn to the closed-loop minimal model of circulatory control displayed in Figure 1. This model is “minimal” in the sense that it is able to account for most of the dynamic features of HRV and yet be simple enough that all its characteristic parameters can be estimated from measurements obtained in an individual subject. This model enables the characterization of the dynamic interrelationships between various pairings of the 3 measured variables: respiration, R-R interval (RRI, ie. the inverse of heart rate), and arterial blood pressure (represented in Fig. 1 as systolic blood pressure, SBP). For instance, fluctuations in RRI (RRI) are assumed to be produced by fluctuations in SBP (SBP) via the baroreflex control of heart rate (“ABR” mechanism) and through direct autonomic coupling between respiration (V) and heart rate (“RCC” mechanism). A portion of the changes in SBP is assumed to be produced by fluctuations in stroke volume due to respiratory modulation of intrathoracic pressure (“direct effects of respiration”). Another contribution to SBP is derived from changes in RRI via the Frank-Starling mechanism and Windkessel “runoff” effect (DeBoer et al., 1987). In this review, however, the focus will be on the determination and characterization of the ABR and RCC mechanisms which give rise to HRV.

Given the model structure as displayed in Figure 1, the mathematical formulation of the respiratory-cardiac coupling (RCC) and baroreflex (ABR) contributions to HRV (ie. RRI) can be written as follows:

$$\Delta RRI(t) = \sum_{\tau=0}^{p-1} h_{RCC}(\tau) \Delta V(t - \tau - T_{RCC}) + \sum_{\tau=0}^{p-1} h_{ABR}(\tau) \Delta SBP(t - \tau - T_{ABR}) + \varepsilon_{RRI}(t) \quad [1]$$

In Equation [1], T_{RCC} and T_{ABR} are the latencies associated with the RCC and ABR mechanisms, respectively, and $\varepsilon_{RRI}(t)$ represents the stochastic component of RRI not accounted for by these two mechanisms. Since the model is assumed to be linear, RCC and ABR dynamics are completely characterized by their respective “impulse responses” (- in the frequency domain, these impulse responses translate to “transfer functions”).

The baroreflex impulse response, $h_{ABR}(t)$, for instance, quantifies the time course of the change in RRI resulting from an abrupt increase in SBP of 1 mmHg. It represents our best estimate of the dynamic response of the heart rate baroreflex after discounting for HRV fluctuations due to respiration. The RCC impulse response, $h_{RCC}(t)$, provides our best estimate of the time course of the fluctuation in RRI in response to a very rapid inspiration and expiration of 1 liter of air, after discounting the contribution to HRV from the baroreflexes.

In general, we have found that both the RCC and ABR impulse responses decay back to baseline within 20 s; thus, in Equation [1], p is assigned a value of 40, given a sampling interval of 0.5 s. The presence of time delays in the model and the use of a time-domain representation allows us to computationally “open the loop” of the closed-loop system, thereby separating the feedforward from the feedback components. Spectral analysis techniques do not permit this kind of temporal delineation. Using measurements of ΔV , ΔSBP and ΔRRI , solution of Equation [1] yields estimates of the unknown impulse responses $h_{RCC}(t)$ and $h_{ABR}(t)$, along with the delays T_{RCC} and T_{ABR} . Details of the estimation algorithm are given in Belozeroff et al. (2002). One other advantage is that this approach allows us to obtain a comprehensive assessment of the primary mechanisms that contribute to heart rate variability and blood pressure variability, using data measured from a single test procedure. Similar approaches, with individual differences in model structure, have been employed in previous studies to investigate cardiovascular variability (Baselli et al., 1988; Mullen et al., 1997; Mukkamala et al., 1999); however, none of these models have been applied to study autonomic control in OSA.

To facilitate statistical comparison, compact descriptors of the magnitude and time-course corresponding to each impulse response are subsequently derived. For instance, the difference between peak overshoot and peak undershoot is used to represent impulse response magnitude. Another descriptor is the characteristic time, which provides a quantification of how sluggish the impulse response is – thus, a short characteristic time would reflect a highly rapid response to the abrupt stimulus. A third descriptor is the “dynamic gain”, which is derived by transforming the impulse response into the equivalent transfer function in the frequency domain and deducing the average gain in the range of frequencies that span the LF and HF regions. The minimal model approach has been applied to datasets obtained in a number of different studies on subjects with OSA and normal controls (Belozeroff et al., 2002; Belozeroff et al., 2003; Jo et al., 2003; Jo et al., 2005; Blasi et al., 2006; Jo et al., 2007; Chaicharn et al., 2009). The findings derived from these analyses are presented below. A brief summary is given in Table 1.

5.1. RCC and ABR dynamics: OSA vs normals

A comparison of respiratory-cardiac coupling (RCC) dynamics between 11 OSA subjects (closed circles) and 11 normal controls (open circles) during wakefulness is displayed in the

top left panel of Figure 2. The general form of the RCC impulse responses in both groups is similar: there is an initial decrease in RRI (or acceleration of heart rate), followed by a subsequent RRI increase (deceleration of heart rate). This is compatible with established observations about the biphasic nature of respiratory sinus arrhythmia: heart rate accelerates primarily during inspiration and decelerates during expiration (Katona and Jih, 1975; Eckberg, 1995). The magnitude of the RCC impulse response in OSA is, on average, about one third the corresponding magnitude in normal controls (OSA: 97.5 ± 36.3 vs Normals: 295.2 ± 88.6 ms L⁻¹, $P=0.001$). As well, the decay of the RCC impulse response back towards baseline is visibly faster in OSA compared to normals. In both subject groups, we have consistently found that the initial negative phase of $h_{RCC}(t)$ occurs approximately 1 s prior to the start of mechanical inspiration. This finding is in agreement with reports from previous studies (Mullen et al., 1997; Saul et al., 1989) that suggest that changes in heart rate briefly precede changes in lung volume. Katona and coworkers (1970) found in recordings of cardiac vagal efferent fibers of anesthetized dogs that vagal firing ceased 0.5 seconds before the onset of respiratory activity. Thus, it appears that there is a neural coupling between the central modulation of heart rate and the drive to breathe which precedes mechanical inspiration.

In both OSA and normals, the cardiac baroreflex (ABR) impulse response exhibits a sharp positive peak between 1 and 2 seconds following an initial latency of ~1 s. This may be followed by a smaller negative undershoot, the magnitude of which varies across individuals and across subject groups. The large initial positive phase of $h_{ABR}(t)$ represents the classic baroreflex-mediated reduction in heart rate (or equivalently, the increase in RRI) that results from a transient increase in arterial blood pressure. ABR impulse response magnitude is significantly lower in OSA versus normals (1.75 ± 0.58 vs 2.85 ± 0.51 ms mmHg⁻¹, $P < 0.02$).

5.2. Effects of orthostatic stress

Changing posture from supine to standing leads to highly substantial changes in the respiratory-cardiac coupling (RCC) and baroreflex (ABR) impulse responses, as shown in Figure 2 (right panels). In both normals and OSA subjects, the RCC impulse response magnitudes are reduced with standing to 97.2 ± 16.3 ms/L in normals and to 37.0 ± 5.2 ms/L in OSA; these are approximately a third of their corresponding values in the supine posture (Fig. 2, top right panel). The impulse responses become less oscillatory, but other than that, the time-courses of these impulse responses are relatively unchanged.

There is a tendency for orthostatic stress to also reduce the magnitudes of the ABR impulse responses in both groups of subjects, but these changes are highly variable across subjects and consequently they do not attain statistical significance (Fig. 2, bottom right panel). However, a noticeable effect of postural change on ABR is a prolongation or broadening of the initial positive phase of the impulse response in both groups of subjects.

The substantially depressed RCC and ABR gains in the OSA subjects vis-à-vis normal controls suggest that there is significant impairment of parasympathetic control of heart rate in OSA. Orthostatic stress depresses RCC gain further in both subject groups, but exerts a much weaker effect on ABR gain. This suggests that the effect on HRV of a reduction in parasympathetic activity accompanying standing may be partially countered by a concomitant increase in sympathetic modulation. The visibly more sluggish ABR impulse responses during standing provide additional evidence of the increased dominance of the sympathetic nervous system over vagal control as a result of orthostatic stress. These observations are compatible with reports by others that support the notion that orthostatic stress leads to sympathetic excitation and vagal withdrawal (ESC/NASPE Task Force, 1996; Montano et al., 1994; Malliani et al., 1991).

In a recent study on obese teenagers, we found measures of insulin resistance to be correlated with desaturation index, a measure of the degree of intermittent hypoxia resulting from OSA (Lesser et al., 2010). These subjects also had detectable impairments in autonomic function. For instance, reactivity of RCC gain to orthostatic stress was reduced in subjects with greater OSA severity (Oliveira et al., 2011). These correlations remained even after adjustments for age and adiposity.

5.3. Effects of long-term CPAP therapy

Figure 3 demonstrates how treatment of OSA using continuous positive airway pressure (CPAP) over an average duration of 6 months can affect autonomic control, as assessed by the RCC and ABR impulse responses. In this case, measurements of respiration, heart rate and noninvasive continuous blood pressure were obtained from 13 middle-aged subjects with moderate-to-severe OSA in supine wakefulness before and after long-term CPAP therapy. Patient compliance with the prescribed treatment ranged widely from 0 to >8 hours per night. For this reason, the subjects were divided into two groups: 6 compliant patients, who used CPAP for an average of >3 hours per night, and 7 non-compliant patients whose average CPAP use was <3 hours per night.

In the compliant group, the respiratory-cardiac coupling (RCC) impulse response magnitude increased almost threefold from 65.8 ± 28.4 ms/L pre-CPAP to 196.7 ± 138.3 ms/L post-CPAP. On the other hand, in the non-compliant group, the RCC impulse response remained unchanged in both shape and magnitude (Fig. 3, top left vs top right panels). The baroreflex (ABR) impulse response magnitude increased from 0.92 ± 0.37 ms/mmHg pre-CPAP to 2.71 ± 1.81 ms/mmHg post-CPAP in the compliant group; however, in the non-compliant group, there was no change. These findings are consistent with the aforementioned results comparing OSA subjects with normal controls. Taken together, they demonstrate that reduced HRV in OSA is due to **both** depressed baroreflex sensitivity and respiratory-cardiac coupling, and that treatment with CPAP can partially reverse these changes. However, the beneficial effect of CPAP depends strongly on patient compliance.

5.4. Changes in autonomic control during sleep

Figure 4 summarizes the results of a study conducted by Jo et al.(2003) on a group of 8 normals and 9 untreated patients with moderate-to-severe OSA patients. Respiration, RRI and continuous blood pressure were measured in relaxed wakefulness, stage 2 and REM sleep. To improve the quality of parameter estimation in the modeling process, random “noise” was added to tidal volume on a breath to breath basis in the following manner. Each subject was connected via nasal mask to a bilevel pressure noninvasive ventilator, which was computer-controlled to deliver inspiratory pressures that varied randomly from breath to breath during the test protocol. In between applications of the test protocols, both expiratory and inspiratory positive airway pressures were set at the CPAP level prescribed for each patient in order to maintain upper airway patency. In the healthy controls, a small level of CPAP of ~2.5 cm H₂O was applied.

As shown in Figure 4 (left panel), respiratory-cardiac coupling (RCC) gain is roughly two-thirds as large in the OSA subjects compared to their normal counterparts over all sleep-wake states. The interesting part of this finding is that RCC gain does not change significantly with sleep in both subject groups. Baroreflex (ABR) gain (Fig. 4, right panel) is also significantly lower in the OSA subjects vis-à-vis the normal controls. However, there is approximately a threefold increase in ABR gain between wakefulness and sleep in normals, whereas the OSA subjects exhibit no significant change. Thus, the effect of sleep on baroreflex sensitivity in OSA is considerably different from that in normals. This is compatible with the study of Parati et al. (1997), who found in 11 OSA subjects and 10

normals, that baroreflex sensitivity increased ~42% from wakefulness to sleep in normals but remained unchanged in OSA. These workers used the sequence technique, in which baroreflex sensitivity is assumed to be the slope of the regression line relating spontaneous changes in SBP to related changes in RRI. This method does not allow for the influence of respiration on the changes in RRI, which may account for the fact that our values of baroreflex sensitivity for both normals and OSA are smaller than those reported by Parati (1997). This systematic discrepancy between the model-based method and sequence method for assessing baroreflex sensitivity has been noted in other studies as well (Patton et al., 1996).

It should be pointed out as well that, in this study, Jo et al.(2003) reported significant increases in HF power of HRV in REM and Stage 2 sleep compared to wakefulness in the healthy controls – consistent with the existing literature (Zemaityte et al., 1984; Lombardi and Parati, 2000). However, the fact that respiratory-cardiac coupling gain remained relatively unchanged with sleep while baroreflex gain increased threefold suggests that the observed increase in respiratory sinus arrhythmia that occurs in sleep is primarily baroreflex-mediated.

5.5. Changes in autonomic control resulting from sleep disruption

The minimal model has also been applied to investigate the cumulative effects of repetitive arousal alone (independent of the hypercapnia and hypoxia associated with obstructive apneas) on cardiovascular autonomic control in healthy young adults (Chaicharn et al., 2008). Ten subjects participated in multiple sleep studies consisting of 4 conditions with 2 nights in each condition. The first was normal sleep where participants were left to sleep undisturbed. In the other three conditions, the subjects were aroused by repetitive auditory stimuli with periodicities of 30 seconds, 1 minute and 2 minutes of sleep. The arousal stimuli were applied over a contiguous duration of 50 minutes in Stage 2 sleep. The minimal model was applied to estimate how the respiratory-cardiac coupling (RCC) and baroreflex (ABR) impulse responses would change pre- vs post-exposure to the arousals.

Repetitive arousal did not produce any cumulative effects on mean RRI or mean SBP. However, analysis of the data using the minimal model revealed more subtle effects. During undisturbed sleep onset, ABR gain increased with increasing depth of sleep, as had been expected. This was also the case with the RCC component, although the effect was substantially greater in the low-frequency region of the associated transfer function. However, both minimal model gains did not change significantly when sleep was interrupted by repetitive arousal. These findings suggest that exposure to repetitive arousal blocks the natural shift during normal sleep onset in sympathovagal balance towards greater vagal predominance and lower sympathetic tone. This cumulative effect on the changes in ABR and RCC gains was not affected by the periodicity with which the arousals were elicited. At the same time, repetitive arousal led to increases in the power of low-frequency blood pressure oscillations, suggesting an accompanying cumulative elevation of sympathetic tone that offsets the tendency for sympathetic withdrawal and vagal dominance that accompanies natural sleep onset.

5.6. Modeling the autonomic effects of arousal

In the afore-mentioned studies, it was assumed that the parameters of the minimal model would be constant over the test duration which ranged from 5 to 10 mins. Since we know that some of the model parameters are altered by sleep-wake state, it is reasonable to expect that the magnitude and/or time-course of their impulse responses might also change transiently during arousals from sleep. Since subjects with OSA are chronically exposed to

repetitive arousals during sleep, a major question is whether this long-term exposure leads to some form of adaptation in the autonomic responses to arousals.

However, in order to track such changes with the model, it is necessary to relax the requirement for stationarity and thus allow for time-varying dynamics of the model components. Mathematically, this is formulated in the following way:

$$\Delta RRI(t) = \sum_{\tau=0}^{p-1} h_{RCC}(t, \tau) \Delta V(t - \tau - T_{RCC}) + \sum_{\tau=0}^{p-1} h_{ABR}(t, \tau) \Delta SBP(t - \tau - T_{ABR}) + \varepsilon_{RRI}(t) \quad [2]$$

Note that, now, the respiratory-cardiac coupling (RCC) and baroreflex (ABR) impulse responses are each shown as functions of two time indices: as in the time-invariant case, τ represents the time index associated with the dynamics of the impulse response, whereas t represents actual time. This statement may appear less confusing if one were to turn to Figure 5 for clarification. Here, “snapshots” of the ABR impulse response before, during and after arousal are displayed. The closed circles with black line represent the form of the ABR impulse response shortly before the arousal stimulus is applied. The red circles and red line represent the ABR impulse response during the arousal. The open circles and green line represent the estimated ABR impulse response in the post-arousal recovery period. Thus, in Fig. 5, the time-axis represents the impulse response lag, τ . And since the ABR impulse response is time-varying, at each time t , ABR assumes a different time profile. The time-varying impulse responses in Equation [2] can be estimated using “adaptive filtering” techniques (Blasi et al., 2006). The time-varying extension of the minimal model has been applied to cardiorespiratory data measured in 8 subjects with untreated OSA and 8 healthy controls during transient arousal from sleep (Blasi et al. 2002, 2006). Transient arousals from sleep in healthy subjects are known to produce brief increases in ventilation, heart rate and blood pressure that accompany large surges in sympathetic drive (Blasi et al. 2003). To dissociate transient state changes from apnea or hypopneas, the experimental protocol involved the generation of arousals through the application of a brief auditory stimulus during sleep (Blasi et al. 2002, 2006). The minimal model was applied to data segments containing respiration, RRI and SBP, recorded before and several minutes after each arousal. Figure 6 shows that the arousal-induced changes in RRI (left panel) and SBP (right panel) during NREM sleep are highly blunted in OSA subjects, compared to normal controls. There are significant differences in RRI between OSA and controls from 2.5 to 6.5 s post-stimulus, while in SBP, differences between the groups are significant between 7.0 and 12.0 s. As illustrated in Fig. 7, arousal leads to a rapid and substantial increase in RCC gain in normals; RCC gain remains above baseline (pre-arousal level) up to 30 s following the start of arousal. In contrast, there is a much smaller and less long-lasting increase in RCC gain in the OSA subjects. In normals, the ABR response to arousal consists of a rapid increase in impulse response magnitude immediately after arousal for up to 10 s post-stimulus (Fig. 7, right panel) with a subsequent undershoot from 15 s to 30 s following the start of arousal. By contrast, in OSA patients, ABR gain remains relatively unchanged during arousal, along a subsequent depression in gain.

The large and almost immediate increase in heart rate that accompanies arousal is often interpreted as a dramatic withdrawal of parasympathetic drive. Our model suggests that this transient increase in heart rate can be accounted for as a secondary effect of the concomitant increase in ventilation that accompanies the arousal. However, the increase in heart rate is substantially larger than would be predicted on the basis of pre-arousal levels of RCC gain. Thus, to account for the observed acceleration in heart rate, the model predicts that RCC gain has to increase transiently. Baroreflex gain is also predicted to increase substantially immediately following the start of arousal. It is unclear at this point why this should be the

case. We speculate that the increase may be a built-in mechanism for buffering the surge in blood pressure that normally accompanies arousal. The lack of these changes in the arousal responses of the OSA subjects suggests that there is an impairment of the sensitivity of the RCC and ABR model components to transient state changes. This impairment may have developed as a consequence of the chronic adaptation of the autonomic cardiovascular system to episodic arousal in OSA.

In addition to the afore-mentioned studies related to arousal, the time-varying version of the minimal model has been applied to track how the autonomic model parameters change during and after cold face stimulation (Chaicharn et al., 2009). The same methodology could also be used to estimate dynamic changes in autonomic function during apneic events throughout the night.

6. Limitations of the Minimal Model

One important limitation of the minimal model, as presented thus far, is the assumption of linearity in the underlying dynamics. This model is able to capture the most salient features of the cardiorespiratory dynamics under study, generally accounting for ~60% of the total variance. However, it is unable to account for the residual fraction of the total variance, particularly dynamics at frequencies below 0.1 Hz. Jo et al. (2007) extended the minimal model by adding nonlinear dynamics using a Volterra-Wiener kernel formulation and the Laguerre expansion technique to estimate the model parameters. The extended model included (a) a nonlinear 2nd order respiratory-cardiac coupling (RCC) component; (b) a nonlinear 2nd order baroreflex (ABR) component; and (c) a component describing the multiplicative interaction of the effects of respiration and blood pressure on heart rate. Application of this extended model to data from normals and a group of subjects with OSA revealed that the OSA subjects had significantly reduced nonlinear ABR and interaction kernel magnitudes. As well, by incorporating the nonlinear and interaction terms, the extended model was able to account for an additional 20% of the total variance.

While the interpretation of the linear RCC and ABR kernels is relatively simple, it is considerably more difficult to understand what the nonlinear kernels represent physiologically. To better understand the significance of our findings, we conducted simulations using the group-averaged nonlinear kernels estimated from the controls and OSA subjects. We found that the nonlinear 2nd order component of RCC dynamics represents the independent effect of tidal volume on RCC gain, such that as tidal volume increases at a given respiratory frequency, RCC gain increases. The nonlinear 2nd order component of ABR dynamics represents the saturation effect on heart rate as the amplitude of the change in blood pressure increases. The interaction kernel was found to represent the effect of respiration on the baroreflex response, such that a brief increase in blood pressure occurring during expiration exerts a greater effect on RRI than a similar pulse occurring during inspiration. All these model predictions are consistent with observations that have been previously established in the literature using more intrusive or invasive methods of probing the human cardiovascular system (Eckberg, 1995). Although the primary focus of the studies discussed above was on the use of the minimal model to delineate the effects on HRV of respiratory-cardiac coupling from those mediated by the baroreflexes, a number of these studies also examined the “other half” of the closed-loop model in which respiration and changes in RRI contribute to blood pressure variability (Fig. 1). RRI and stroke volume, along with total peripheral resistance, determine the value of SBP on a beat-to-beat basis. There is also some contribution from respiration through direct mechanical effects and, also possibly respiration-synchronous sympathetic activity, on stroke volume. However, a key problem here is that the resulting equation for SBP variability (analogous to that for HRV as represented by Eq. 1) is much harder to solve, given that some of the important auxiliary

variables, eg. stroke volume and total peripheral resistance, are generally not available from invasive measurements. On the other hand, knowledge of the interrelationships between some of these variables, eg. SBP and total peripheral resistance, could provide useful information about sympathetic control of the peripheral vasculature. Preliminary work in this direction utilizing peripheral arterial tonometry measurements appears promising (Chalacheva and Khoo, 2013).

7. Conclusions

In summary, we have presented an overview of our current understanding of the long-term effects of OSA on cardiovascular autonomic function in humans, focusing directly on the knowledge derived from noninvasive measurements of heart rate, beat-to-beat blood pressure (BP), and respiration during wakefulness and sleep. While spectral analysis of heart rate variability and blood pressure variability has proven to be a useful tool for noninvasively exploring cardiovascular autonomic control, there are serious limitations that are often overlooked, such as the inter- and intra-subject variability in respiratory frequency and ventilatory pattern during natural spontaneous breathing during sleep. The multivariate modeling approach circumvents these problems by focusing on characterizing the dynamic interrelationships between various pairings of the three measured variables: respiration, heart rate, and arterial blood pressure. At the same time, the “minimal” model that is derived from these three noninvasive measurements is limited in that it does not permit a mathematical representation of other factors, not currently measured, that contribute to blood pressure variability, such as the sympathetic control of peripheral vascular resistance or sympathetic control of cardiac contractility. Work to extend the model in these directions is ongoing.

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Highlights

- This paper reviews current knowledge of the long-term effects of obstructive sleep apnea (OSA) on cardiovascular autonomic function in humans.
- There are serious limitations with the conventional time-domain and spectral methods of heart rate variability analysis.
- A multivariate dynamic model relating heart rate variability to blood pressure and respiration is employed.
- Respiratory-cardiac coupling and baroreflex function are impaired in OSA, as well as the responses to arousal from NREM.

Figure 1.

Schematic block diagram of the closed-loop minimal model of cardiovascular variability. RCC and ABR are the main model components that mediate heart rate variability; other factors are represented as “extraneous influences on RRI”. The “other half” of the closed-loop model consists of the components responsible for generating blood pressure variability.

Figure 2. Averaged impulse responses (with standard error bars) of the RCC (top panels) and ABR (bottom panels) model components estimated for patients with moderate-to-severe OSA (closed circles) and normal controls (open circles) in the supine (left panels) and standing (right panels) postures. Modified with permission from Belozeroff et al., *Sleep*, 2003.

Figure 3.

Averaged impulse responses (with standard error bars) of the RCC (top panels) and ABR (bottom panels) model components estimated from patients with moderate-to-severe OSA during supine wakefulness, before (closed circles) and after (open circles) undergoing long-term CPAP therapy. The left panels display results for the group of patients who were compliant with therapy (ie. nightly CPAP use > 3 h), whereas the right panels represent the group that was not compliant with treatment (ie. nightly CPAP use < 3 h). Reproduced with permission from Belozeroff et al., *Am J Physiol*, 2002.

Figure 4.

Comparison of RCC (left panel) and ABR (right panel) gains between OSA subjects (open triangles) and normal controls (closed circles) across wakefulness, rapid eye movement (REM) sleep, and non-REM Stage 2 sleep. Reproduced with permission from Jo et al., *Am J Respir Crit Care Med*, 2003.

Figure 5.

“Snapshots” demonstrating the time-varying nature of the ABR impulse response in a normal subject shortly before arousal (thick black line, closed circles), during arousal (thin grey line, closed grey circles) and after arousal (thin black line, open circles).

Figure 6. Time courses of changes (expressed as percent of pre-arousal baseline levels) in RRI (left panel) and SBP (right panel) following acoustically-induced arousal from NREM sleep in OSA subjects (open circles) and normal controls (closed circles).

Figure 7.

Time courses of changes (in percent of pre-arousal baseline levels) in the impulse response magnitudes of the RCC (left panel) and ABR (right panel) model components before, during, and after acoustically-induced arousal in OSA subjects (open circles) and normal controls (closed circles).

TABLE 1

Summary of Key Studies using the Minimal Model

Study (published reference)	Model Version & Features	Subject Pool & Study Conditions	Summary of Findings
Belozeroff et al. (2002)	Original Minimal Closed-loop Model	OSA subjects studied in wakefulness before and after long-term CPAP therapy; comparison of compliant vs. non-compliant subjects	RCC and ABR gains increased while DER (direct effect of respiration) and CID (circulatory dynamics) gains decreased in compliant subjects; CID gain showed a tendency to increase in non-compliant subjects
Belozeroff et al. (2003)	Original Minimal Closed-loop Model	OSA subjects and normal controls studied during wakefulness in supine & standing postures	Reduced ABR and RCC gains, but higher CID gain in OSA subjects; both groups show decreases in ABR and RCC gains and increases in CID gain with change in supine to standing
Jo et al. (2003)	Original Minimal Closed-loop Model	OSA subjects and healthy controls studied during wakefulness and sleep under bilevel pressure ventilation (used to broaden bandwidth of breathing pattern)	RCC and ABR gains lower in OSA subjects vs normal controls; RCC gain unchanged with sleep in both groups; ABR gain increased with sleep in normals but remained unchanged in OSA subjects
Jo et al. (2007)	Nonlinear dynamics added to RCC and ABR components; assumed interaction between RCC and ABR gains	OSA subjects and normal controls studied during wakefulness and sleep under bilevel pressure ventilation (used to broaden bandwidth of breathing pattern)	Nonlinear ABR gain and magnitude of interaction between ABR and RCC lower in OSA subjects in all sleep-wake states
Blasi et al. (2002, 2006)	Time-varying dynamics incorporated into all components of minimal closed-loop model	Responses to acoustically-induced arousals studied in normal and OSA subjects during NREM and REM sleep	RCC gain increased during arousal in NREM but not in REM sleep; ABR gain increased transiently during arousal in both sleep states but subsequently fell below pre-arousal levels. No significant changes in RCC and ABR gains with arousal in OSA subjects.
Chaicharn et al. (2009)	Original and Time-Varying Versions of Minimal Closed-loop Model	Pediatric subjects with OSA and age-matched healthy controls studied during wakefulness	ABR gain lower in OSA subjects, but no differences with controls in gains of other model components; Postural change from supine to standing led to decreases in ABR gain in controls only.