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MODEL-DERIVED MARKERS OF AUTONOMIC CARDIOVASCULAR DYSFUNCTION IN SLEEP-DISORDERED BREATHING

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Abstract

A large body of evidence indicates that sleep-disordered breathing leads to abnormally elevated sympathetic tone and impaired vagal activity, and that these factors in turn promote hypertension and cardiometabolic disease. Thus, low-cost but accurate monitoring of autonomic function is useful for the aggressive management of patients with sleep apnea. However, the mechanistic information that can be derived from conventional noninvasive techniques, such as heart rate variability, is limited by the univariate nature of the underlying analyses. This article reviews the development and application of multivariate dynamic biophysical models that enable the causal dependencies among respiration, blood pressure, heart rate variability and peripheral vascular resistance to be quantified. The markers derived from these “minimal models” can be used in conjunction with heart rate variability to increase the sensitivity with which abnormalities in autonomic cardiovascular control are detected in subjects with sleep-disordered breathing.

Keywords

heart rate variability; cardiorespiratory control; minimal model; sleep apnea; peripheral vascular resistance

INTRODUCTION AND BACKGROUND

Several large epidemiological studies have suggested that sleep-disordered breathing (SDB), which occurs most commonly in the form of obstructive sleep apnea (OSA), constitutes an independent risk factor for the development of a wide range of cardiovascular diseases.^{1,2} For instance, the Wisconsin Sleep Cohort Study, with over 700 subjects, demonstrated that the adjusted odds ratio of incident systemic hypertension in SDB subjects with respiratory disturbance index (RDI) > 15 was almost three times higher relative to subjects without SDB.³ In the Sleep Heart Health Study cohort of 6,132 subjects, SDB was found to be strongly correlated with coronary heart disease, heart failure and stroke.⁴ Nieto et al.⁵ found

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the odds ratio of hypertension to increase with severity of SDB. Studies employing animal models have been useful in suggesting causal links between the key acute effects of SDB – intermittent hypoxia and sleep disruption – and its chronic cardiovascular sequelae.⁶ Brooks et al.⁷ were able to produce nocturnal and daytime hypertension by exposing a dog model to sleep-triggered periodic airway obstructions for several weeks. On the other hand, sustained exposure to periodic acoustically-induced arousals without accompanying airway obstruction in these animals produced only nocturnal hypertension with no carry-over effect in the daytime. In a rat model, Fletcher et al.^{8,9} found that sustained hypertension developed after a few weeks of exposure to intermittent hypoxia without any accompanying upper airway obstruction.

There are a number of mechanisms through which intermittent hypoxia, produced by SDB, can lead to hypertension and other forms of cardiovascular disease, but abnormal autonomic control appears to play a major role.^{10,11} Studies utilizing peroneal microneurography or testing of plasma catecholamines have shown that sympathetic tone is abnormally high in subjects with SDB in both sleep and wakefulness.^{12,13} Narkiewicz et al.¹⁴ compared obese adult subjects with and without SDB and showed that obesity alone, in the absence of SDB, was not accompanied by increased muscle sympathetic nerve activity. Treatment with continuous positive airway pressure (CPAP) partially reverses these effects.^{15–18}

To determine whether the abnormal autonomic control is causally related to the exposure to intermittent hypoxia, several prospective studies in normal humans have been carried out. Xie et al.¹⁹ found that exposing healthy young subjects to intermittent asphyxia over a period of 20 min led to sympathetic activation that continued even after the stimulus was removed. In another study, prolonged sympathetic activation was produced after 20 min exposure to intermittent hypoxic apnea.²⁰ 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. Healthy young subjects exposed to repetitive hypoxic apneas displayed small post-recovery elevations in mean arterial blood pressure, along with a more sustained and substantial increase in muscle sympathetic nerve activity.^{21,22} Baroreflex impairment resulting from SDB could also be involved in the development of altered vasoconstrictor function and systemic hypertension.²³ Narkiewicz and colleagues²⁴ found abnormal baroreflex sympathetic modulation in subjects with SDB. Our own studies have shown reduced baroreflex control of heart rate in patients with SDB,²⁵ which was partially restored following long-term CPAP therapy.²⁶

“SIGNALS” vs. “SYSTEMS” ANALYSIS

The association between SDB and autonomic dysfunction suggests that the monitoring of the relevant autonomic variables may constitute a useful means of tracking the development of the disorder over time in individual subjects. Peroneal microneurography provides the most direct measurement of muscle sympathetic nerve activity, but the method is impractical in terms of clinical utility since it requires considerable technical expertise and is highly susceptible to artifactual noise introduced by limb movements.²⁷ Plasma or urinary catecholamine concentrations provide an integrated measure of sympathetic outflow over a

period of many hours, and as such, are limited in sensitivity and temporal resolution.²⁸ Cardiovascular stress tests are relatively easy to administer clinically, but they have been shown to be rather insensitive and require subject cooperation, which is not possible during sleep.²⁹

Assessment of autonomic nervous system activity using heart rate variability (HRV) has attained widespread popularity due to 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. The present consensus is that only parasympathetic (vagal) activity accounts for the contribution to the high-frequency (HF, 0.15–0.4 Hz) component of HRV.³⁰ 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.³¹ The ratio between LF and HF spectral powers has been used by researchers broadly as an index of ‘sympathovagal balance’.³² The premise that HRV can provide useful indices of cardiac autonomic control may be traced back to Katona and Jih,³³ who demonstrated, in an anesthetized dog preparation, a linear relationship between vagal firing rate and R-R interval (RRI), the inverse of beat-to-beat heart rate. Their finding was obtained under conditions in which respiration was relatively well-controlled. Subsequent studies extended this notion to humans and pharmacological interventions were employed to alter the relative importance of sympathetic versus vagal modulation of heart rate. In these studies, respiration was either controlled or kept relatively uniform while vagal activity was altered. However, the natural variability in respiration, particularly during changes in sleep-wake state, can seriously confound the presumed simple relationship between RRI and vagal traffic.^{34,35} Moreover, changes in ventilation and ventilatory pattern can alter autonomic input to the heart via chemoreceptor feedback. As well, changes in breathing alter vagal feedback from the lungs, and this has been shown to influence sympathetic activity.

Another major drawback of employing HRV alone to assess autonomic function is that one can only derive from this information the net effect of all the factors that contribute to heart rate control, thus providing little insight into the underlying physiological mechanisms. One way of overcoming the limitations inherent in univariate signal analysis is to measure other related signals in parallel and to employ multivariate analysis to determine how each signal may be related to the others. A prime example is the “alpha index”, which represents the gain of the transfer function relating blood pressure variability (or more specifically, changes in systolic blood pressure) to changes in RRI. Thus, instead of deriving information from HRV or blood pressure variability as individual signals, this “systems” approach allows us to extract the dynamic properties of the “black box” that relates fluctuations in RRI to fluctuations in blood pressure. However, although the alpha index is frequently employed as a measure of baroreflex sensitivity,³⁶ this presumption ignores the fact that RRI and blood pressure are physiologically coupled to one another in a closed-loop system: changes in blood pressure produce changes in RRI via the baroreflexes, but changes in RRI can also lead to changes in blood pressure through variations in cardiac output via Starling’s law and the Windkessel effect.³⁷ Moreover, since the alpha index represents a one-input one-output system (blood pressure to RRI), it also does not include the effects of other inputs, such as respiration. Thus, in order to take into account multiple inputs and feedback in a given system, it is necessary to formulate a model that contains explicit functional pathways that

reflect physiological dependencies among the various variables (e.g. RRI, blood pressure, respiration). Each component in this model can have multiple inputs but the dynamics between each input and the output must be “causal” – i.e. changes in the output at the present time can only be ascribed to changes in one or more of the inputs that occurred in the past. Moreover, such a model would be labeled a “minimal model”, if it is able to account for most of the dynamic features of a set of physiological responses and yet be simple enough that all its characteristic parameters can be estimated from measurements obtained in individual subjects.

MODEL-DERIVED MARKERS OF HEART RATE VARIABILITY

Based on our knowledge of the underlying physiology, RRI, respiration and systolic blood pressure (SBP) are assumed to be interrelated through the closed-loop control scheme illustrated in Fig.1. Respiration influences RRI directly through autonomic respiratory-cardiac coupling. The latter includes the mechanisms responsible for central respiratory entrainment of the cardiovagal motoneurons in the medulla as well as vagal feedback from the pulmonary stretch receptors.³⁸ Respiration also affects RRI indirectly through changes in intrathoracic pressure, which are translated into changes in blood pressure; the latter subsequently stimulate the baroreceptors, leading to fluctuations in RRI. The totality of these respiratory influences on heart rate variability constitutes respiratory sinus arrhythmia. The “closed-loop” nature of the control scheme derives from the fact that changes in RRI, along with changes in stroke volume (not measured), lead to fluctuations in cardiac output that, in turn, produce fluctuations in SBP. Apart from intrathoracic pressure changes and changes in cardiac output, fluctuations in SBP can also arise from other sources of spontaneous variability, such as sympathetically-driven variations in peripheral vascular resistance. The part of this closed-loop circulatory control model that accounts for HRV is represented as the area circumscribed by the box (broken lines) displayed in Fig.1. Fluctuations in RRI (ΔRRI) are decomposed into 3 components: the first arising from direct respiratory-cardiac coupling (“RCC”), the second from stimulation of the baroreflexes (“ABR”) by variations in blood pressure (ΔSBP), and the third from spontaneous variations not related to respiration (ΔV) or the baroreflexes (“extraneous influences on RRI”).

Thus, the HRV part of the model can be characterized mathematically as:

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

where $\varepsilon_{RRI}(t)$ represents the totality of contributions to $\Delta RRI(t)$ not accounted for by the postulated mechanisms, including random noise. The dynamics of the RCC and ABR mechanisms are represented by their corresponding impulse responses $h_{RCC}(\tau)$ and $h_{ABR}(\tau)$, which may also include latencies embedded in the responses. In linear systems theory, the impulse response provides a complete characterization of the dynamic properties of the system in question, since the response of this system to any arbitrary input can be predicted by mathematically convolving the input with the impulse response.³⁹ $h_{ABR}(\tau)$, for instance, quantifies the time-course of the change in RRI resulting from an abrupt increase in SBP of

1 mmHg, whereas $h_{RCC}(\tau)$ quantifies the time-course of the fluctuation in RRI associated with a very rapid inspiration and expiration of 1 liter of air. It is important to note that, since respiration, RRI and SBP are measured, it is possible to estimate both model impulse responses from the data. The impulse responses are assumed to be of finite duration (p sampling intervals). An important feature of this model is that its causal structure allows us to computationally “open the loop” of the closed-loop system (see Fig.1), thereby separating the feedforward (i.e. how RRI depends on SBP) from the feedback (i.e. how SBP depends on RRI) components. Frequency-domain techniques, using spectra derived from RRI and SBP, do not permit this kind of temporal delineation, but this problem is circumvented by solving for the impulse responses in Equation (1) in the time domain, with the accompanying constraint that these impulse responses have to be causal.³⁹

The minimal model presented here may be considered “kernel-based”, since the dynamics of its major components are explicitly characterized by their corresponding impulse responses which are estimated from the data. This contrasts with the more traditional approach in which the dynamics are more compactly described using differential equations with unknown coefficients that represent the parameters to be estimated. In order to reduce the level of parametrization and thus increase estimation accuracy, the impulse response of each model component is constructed from the sum of weighted basis functions:

$$h_{ABR}(\tau) = \sum_{j=0}^{q-1} c_j^{ABR} B_j(\tau) \quad (2)$$

where the $B_j(\tau)$ represents the j -th order orthonormal basis function, and c_j^{ABR} are the corresponding unknown weights that are assigned to $B_j(\tau)$ in the ABR impulse response, with q being the total number of basis functions employed. $B_j(\tau)$ may take the form of the Laguerre⁴⁰ or Meixner⁴¹ set of functions. The important practical advantage of this computational feature is that these basis functions are predefined, and thus the only unknown parameters that need to be estimated are the weights c_j^{ABR} . This simplification can produce a substantial reduction in complexity of the estimation process, from p to q , where $p \gg q$, thereby allowing greater statistical reliability to be achieved in the parameter estimates. The reduction in number of parameters estimated is generally on the order of tenfold. Details of this kernel expansion method are given in Belozeroff et al.²⁵ for Laguerre basis functions and Chaicharn et al.⁴² for Meixner basis functions. This “minimal model” approach allows us to obtain a comprehensive assessment of the primary mechanisms that contribute to HRV, using data measured from a single test procedure lasting between 5 and 10 minutes. Similar approaches, with individual differences in model structure, have been employed to investigate the control of heart rate and blood pressure;^{43–45} however, none have been applied to analysis of autonomic control in SDB.

An alternative “minimalist” approach is the technique, first introduced by Thomas et al.,⁴⁶ that extracts information derived solely from the electrocardiogram. In addition to RRI, breathing-related fluctuations in the amplitude of the R-waves are extracted from the ECG and employed to represent respiration. Using an algorithm based on the Fourier transform,

the strength of the correlation between the component oscillations of the RRI and derived respiration signal is computed and used for quantifying “cardiopulmonary coupling” over a broad range of frequencies. The relative predominance of low-frequency (0.01–0.1 Hz) versus high-frequency (0.1–0.4 Hz) cross-spectral power during sleep has been found to be associated with higher prevalence of hypertension and stroke in patients with SDB.⁴⁷ This approach quantifies cardiorespiratory coupling in the frequency domain, whereas our approach employs a parametric model that is estimated in the time domain. One drawback of the cardiopulmonary coupling technique is that it does not explicitly take into account the component of RRI variability that is mediated by the baroreflexes.

Derivation of Model-based “Markers”

In the minimal model of HRV, following the estimation of each model impulse response, its corresponding frequency-domain characteristics (i.e. its transfer function) can be computed by applying the fast Fourier transform to the impulse response. Compact descriptors of the estimated impulse response or transfer function are subsequently extracted, allowing for statistical comparison across individual or group datasets. These descriptors constitute the model-derived markers associated with the dynamic model that best represents autonomic control under a certain set of conditions (e.g. disease vs. no disease, predominantly sympathetic vs. predominantly vagal, etc.). 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. In our previous work, these descriptors generally consisted of: 1) the low-frequency (LF) gain, the average transfer function magnitude between 0.04–0.15 Hz; 2) the high-frequency (HF) gain, the average transfer function magnitude between 0.15–0.4 Hz; and 3) the overall dynamic gain, the average transfer function magnitude between 0.04–0.4 Hz.

Application of HRV Minimal Model to SDB: Summary of Results

The studies that we have conducted with the minimal model suggest that it provides a clearer and more mechanistic delineation of sympathetic versus vagal influences on heart rate control than univariate analyses of HRV. For example, an increase in LF and/or HF gains of the RCC component would be consistent with an increase in vagal tone. Reduced ABR gain would be consistent with elevated sympathetic tone and/or a decrease in vagal tone. This inference is compatible with other studies that have demonstrated impaired baroreflex function in essential hypertension,⁴⁸ congestive heart failure⁴⁹ and following myocardial infarction⁵⁰ – all conditions in which sympathetic tone is abnormally elevated. Whether baroreflex dysfunction leads to abnormally high sympathetic tone or chronic exposure to elevated sympathetic drive leads to depressed baroreflex gain remains unresolved at the present time; nevertheless, there is ample evidence that suggests a strong association between depressed baroreflex gain and high sympathetic tone.⁴⁹ The studies we have performed on human subjects with SDB under a variety of conditions point to a reduction in vagal tone and elevation of sympathetic drive, as detailed below:

- a. Patients with moderate-to-severe OSA (apnea-hypopnea index > 20) and normal controls were studied during wakefulness under spontaneous breathing conditions in both supine and standing postures. ABR and RCC gains were lower in the SDB subjects relative to controls, and both gains decreased significantly from supine to standing postures.²⁵ The finding of reduction in gains with orthostatic stress is consistent with the well-known observation that changing posture from supine to standing leads to greater sympathetic dominance and decreased vagal modulation of the heart.
- b. Patients with moderate to severe OSA were evaluated during wakefulness before and after long-term (~6 months) home continuous positive pressure (CPAP) therapy. In order to enhance parameter estimation accuracy, the subjects were asked to track a randomized breathing pattern displayed on a monitor. The RCC and ABR gains increased approximately threefold after therapy in the subjects who used CPAP consistently for >3 hours per night, but remained unchanged in those patients who were not compliant with therapy.²⁶
- c. Application of the minimal model has also been extended to subjects during sleep.⁵¹ A bilevel pressure ventilator was used in assist mode to increase ventilatory variability in the sleeping SDB subjects. As in the aforementioned studies, both RCC and ABR gains were lower in SDB subjects. However, RCC gain did not change significantly with sleep-wake state in both SDB and control groups, whereas ABR gain increased approximately threefold during sleep (vs. wake) in normal but remained unaffected by state changes in the SDB subjects (Fig.2). These findings imply that the degree of impairment in baroreflex gain in SDB is greater during sleep compared to wakefulness.
- d. The minimal model has been applied to assess autonomic control in children with SDB.⁵² Mean heart rate, mean blood pressure, HRV and blood pressure variability were found to be not significantly different between SDB and control subjects. However, ABR gain was found to be almost half as large in SDB vs. controls, while the differences in RCC gain were not significant. Change in posture from supine to standing led to significant reductions in ABR and RCC gains in both subject groups. Thus, the autonomic effects of SDB on children appear to be different from those reported in adults. Unlike the adult form, there appears to be no significant impairment of parasympathetic function in pediatric SDB, as evidenced by the relatively normal RCC impulse response.
- e. Compared to age-matched normal controls, children with congenital central hypoventilation syndrome (CCHS) were found to have substantially lower overall HRV. On the other hand, there were no differences in mean heart rate, blood pressure or blood pressure variability. Application of the minimal model led to the finding that ABR gain during supine wakefulness was almost sevenfold lower in CCHS relative to normal.⁵³ Orthostatic stress led to a further reduction in the ABR gain of both groups of subjects, even in CCHS subjects whose ABR gain was already low. CCHS subjects also had lower baseline RCC gains relative

to normal, but in both groups, RCC gain declined with change in posture from supine to standing.

- f. 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 autonomic control.⁵⁴ Healthy young adults were aroused from sleep by repetitive auditory stimuli 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.

Markers Derived from Extended Minimal HRV Model

The minimal HRV model has been extended to incorporate potential nonlinearities in the dynamics of the autonomic modulation of heart rate.⁵⁵ In addition to the linear RCC and ABR components displayed in Equation (1), the extended model includes (a) a nonlinear component characterizing second-order RCC dynamics, $h_{2RCC}(\tau_1, \tau_2)$; (b) a nonlinear component characterizing second-order ABR dynamics, $h_{2ABR}(\tau_1, \tau_2)$; and (c) a component describing the multiplicative interaction of the effects of respiration and blood pressure on heart rate, $h_{RCC.ABR}(\tau_1, \tau_2)$. The complete mathematical formulation of this extended model is:

$$\begin{aligned} \Delta RRI(t) = & \sum_{\tau=0}^P h_{RCC}(\tau) \Delta V(t-\tau) + \sum_{\tau=0}^P h_{ABR}(\tau) \Delta SBP(t-\tau) \\ & + \sum_{\tau_1=0}^P \sum_{\tau_2=0}^P h_{2RCC}(\tau_1, \tau_2) \Delta V(t-\tau_1) \Delta V(t-\tau_2) \\ & + \sum_{\tau_1=0}^P \sum_{\tau_2=0}^P h_{2ABR}(\tau_1, \tau_2) \Delta SBP(t-\tau_1) \Delta SBP(t-\tau_2) \\ & + \sum_{\tau_1=0}^P \sum_{\tau_2=0}^P h_{RCC.ABR}(\tau_1, \tau_2) \Delta V(t-\tau_1) \Delta SBP(t-\tau_2) + \varepsilon_{RRI}(t). \end{aligned} \quad (3)$$

While the nonlinear terms in Equation (3) may look abstract and formidable, each of these components has an interpretation that corresponds to observations described in the physiological literature. The nonlinear second-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.⁵⁶ 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, a well known characteristic of baroreceptor function.⁵⁷ The “cross-kernel”, $h_{RCC.ABR}(\tau_1, \tau_2)$, represents the respiratory modulation of baroreflex gain, such that a brief increase in blood pressure occurring during expiration exerts a greater effect on RRI than a similar pulse occurring during inspiration, an observation first described by Eckberg and Orshan.⁵⁸ The simplest “marker” that can be derived from these nonlinear components is the kernel magnitude, defined as the difference between maximum and minimum values of each estimated second-order kernel.

Application of the extended model to data from normals and subjects with SDB revealed significantly reduced nonlinear ABR and interaction kernel magnitudes in SDB, while the nonlinear RCC component was relatively unchanged. In particular, the nonlinear ABR kernel magnitude was substantially lower in SDB relative to controls. This parameter increased from wakefulness to sleep (by almost twofold during stage 2 sleep) in the control group, while it was almost unchanged in the OSAS group. These findings and the results from the linear ABR gains indicate that the arterial baroreflex mechanism, which becomes stronger during sleep in normals, is impaired and does not adapt accordingly during sleep in subjects with SDB.

MODEL-DERIVED MARKERS OF PERIPHERAL VASCULAR CONTROL

Although the primary focus of the studies discussed above was on the use of the minimal model to partition HRV into functional components representing respiratory-cardiac coupling and baroreflex-mediated modulation, 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, e.g. stroke volume and total peripheral resistance, are generally not available from the noninvasive measurements that are made in the clinical setting. On the other hand, knowledge of the interrelationships between some of these variables, e.g. SBP and total peripheral resistance, could provide useful information that relates more specifically to sympathetic control of the peripheral vasculature.

Continuous Measurement of Peripheral Vascular Conductance

While there are a number of methods for assessing vascular resistance, an increasingly popular tool employed in the sleep laboratory is peripheral arterial tonometry (PAT), which measures the fluctuations in digit blood volume using a finger plethysmograph coupled to a constant volume, variable pressure pneumatic system.⁵⁹ Reductions in beat-to-beat amplitude of these fluctuations reflect peripheral vasoconstriction, which is modulated by the sympathetic nervous system. Profound peripheral vasoconstriction resulting from sympathetic surges, following upper airway obstruction and arousal from sleep, constitutes the basis of employing PAT for detection of OSA. By measuring peripheral vascular

responsiveness at the finger tip, which has high density of α -sympathetic innervation and high degree of blood flow rate lability, Schnall and co-workers⁵⁹ found that the blood flow patterns to be associated with apneas, thus serving as markers of the occurrence and severity of the apneas. Another study investigated the effect of upper airway obstruction and arousal on PAT in subjects with OSA.⁶⁰ The amplitude of the within-beat fluctuations in the continuous PAT signal was employed an indicator of vasoconstriction, which was reported to be associated with an increase in sympathetic nerve activity and upper airway obstruction that terminates with arousal. They found that PAT amplitude was significantly reduced as a consequence of airflow obstruction. In addition, periods of induced airflow obstruction that resulted in arousal would even further decrease the beat-to-beat amplitude of the PAT signal. Since a reduction in the amplitude of the PAT signal (PATamp) represents peripheral vasoconstriction, it would appear reasonable to employ PATamp as a surrogate measure of peripheral vascular **conductance**, G_{PV} , the inverse of peripheral vascular resistance.

Minimal Model of Peripheral Vascular Conductance

It is well known that total peripheral resistance is modulated by sympathetically-mediated changes in vascular tone driven by baroreceptor feedback generated by changes in blood pressure. Since G_{PV} , as approximated by PATamp, provides only a regional component of systemic vascular conductance, one would expect that G_{PV} is modulated by local factors in addition to the baroreflex control of sympathetic outflow to the peripheral vasculature. For instance, blood pressure fluctuations at the level of the finger could affect local blood flow through changes in endothelial function.⁶¹ As well, previous reports have indicated the presence of strong respiratory modulation of muscle sympathetic nerve activity measured from peroneal nerve.⁶² Moreover, a deep breath or a sigh has been reported to trigger peripheral vasoconstriction,^{63,64} which further suggests a modulatory influence of respiration on G_{PV} . We have found through a closed-loop simulation model of blood pressure variability that this sigh-vasoconstriction response cannot be reproduced without incorporating a direct respiratory modulation effect on total peripheral resistance.⁶⁵ Thus, with these considerations in mind, we have proposed the following minimal model of peripheral vascular conductance:

$$\begin{aligned} \Delta G_{PV}(t) = & \sum_{\tau=0}^P h_{RPC}(\tau) \Delta V(t-\tau) + \sum_{\tau=0}^P h_{BPC}(\tau) \Delta BP(t-\tau) \\ & + \sum_{\tau_1=0}^P \sum_{\tau_2=0}^P h_{2RPC}(\tau_1, \tau_2) \Delta V(t-\tau_1) \Delta V(t-\tau_2) \\ & + \sum_{\tau_1=0}^P \sum_{\tau_2=0}^P h_{2BPC}(\tau_1, \tau_2) \Delta BP(t-\tau_1) \Delta BP(t-\tau_2) \\ & + \sum_{\tau_1=0}^P \sum_{\tau_2=0}^P h_{RPC,BPC}(\tau_1, \tau_2) \Delta V(t-\tau_1) \Delta BP(t-\tau_2) + \varepsilon_{GPV}(t). \end{aligned} \quad (4)$$

Equation (4) is similar in structure to the extended model of HRV (as defined by Equation (3)) and is shown schematically in Figure 3. The left panels of Figure 3 display an example of the inputs, beat-to-beat pressures (BP) and respiration (ΔV), and output, beat-to-beat PATamp (taken to represent G_{PV}). Changes in peripheral vascular conductance, G_{PV} , are postulated to result from the linear and nonlinear quadratic effects of influences from

respiration, fluctuations in blood pressure, and the interaction between these 2 inputs. In Equation (4), h_{BPC} and h_{2BPC} respectively represent the (linear) impulse response and nonlinear kernel of the effect of blood pressure fluctuations on G_{PV} . h_{RPC} and h_{2RPC} correspond to the impulse response and nonlinear kernel characterizing the dynamics of G_{PV} in response to respiration. $h_{BPC,RPC}$ represents the dynamics resulting from the interaction of blood pressure and respiration. The final term in Equation (4), e_{GPV} , represents all extraneous influences on G_{PV} that cannot be explained by the model. As in the minimal model of HRV, compact descriptors are extracted from the magnitudes and shapes of the estimated impulse responses and nonlinear kernels, and used as the “markers” of the autonomic mechanisms responsible for regulating peripheral vascular conductance.

Application of Minimal Model of G_{PV} to SDB

Since the minimal model of peripheral vascular conductance is a relatively recent development, there have been fewer published applications of this methodology.^{66,67} In the study of Chalacheva and Khoo,⁶⁶ obese adolescents participated in a study that included: 1) noninvasive measurements during wakefulness of respiratory airflow, ECG, continuous blood pressure and PAT during supine and standing postures (10-min recording per posture); 2) morning fasting blood samples, followed by a frequently sampled intravenous glucose tolerance test; and 3) prior night polysomnography. To investigate the combined effect of SDB and insulin resistance (IR) on autonomic reactivity due to orthostatic stress, the subjects were divided into 2 groups (controls vs. SDB+IR) based on their obstructive apnea hypopnea index and insulin sensitivity. “Autonomic reactivity” was quantified as the change in BPC or RPC gains from supine to standing. Overall, the linear and nonlinear gains derived from the minimal model decreased from supine to standing. The SDB+IR group displayed markedly larger reductions in BPC linear and nonlinear gains from supine to standing compared to the control subjects. Fig. 4 displays how the nonlinear BPC gain changed with orthostatic stress on an individual subject-by-subject basis as well as on a group basis (controls vs. SDB+IR). Thus, in the SDB+IR subjects, there was a substantially larger reduction in the nonlinear contribution to baroreflex gain due to change in posture from supine to standing. The physiological basis of this difference in orthostatic response remains unclear at this point, but the ability of the minimal model to detect this difference in response between the subject groups suggests the possibility of employing model-derived markers to monitor the progression of autonomic dysfunction in individual subjects with SDB and/or metabolic syndrome.

SURROGATE OF CONTINUOUS BLOOD PRESSURE

An important limitation on the practical utility of employing the aforementioned minimal models is the need for noninvasive measurement of continuous blood pressure, which is highly expensive and thus problematic for deployment in large scale clinical studies. On the other hand, pulse plethysmography is routinely measured. The speed at which the arterial pressure pulse travels is directly proportional to blood pressure, assuming constant elasticity of the arterial wall. Although pulse transit time (PTT) is not a reliable predictor of systolic blood pressure, there is a good correlation between beat-to-beat fluctuations in PTT (PTTV) and the variability in SBP.⁶⁸ We have taken advantage of this observation to introduce a

surrogate measure of baroreflex gain, BRS_{PTT} , that is derived from HRV and PTTV, and we have demonstrated that BRS_{PTT} correlates robustly with corresponding measures of baroreflex gain derived from noninvasive continuous measurement of arterial blood pressure.⁶⁹ BRS_{PTT} provides information that complements the results derived from HRV alone; in particular, this index provides an indication as to whether the detected differences in HRV could be the result of alterations in baroreflex function. Since the baroreceptors continuously inhibit sympathetic efferent activity, depressed BRS_{PTT} can indicate sympathetic overactivity. Using data derived from polysomnograms in a large-scale study of sleep apnea, we have found that BRS_{PTT} is correlated with measures of impaired glucose tolerance, in subjects with or without SDB.⁷⁰ This association suggests that these low-cost, noninvasively derived autonomic indices may be useful in practice as biomarkers of abnormal glucose metabolism or autonomic dysfunction.

SUMMARY

In this paper, we have presented a comprehensive, but nevertheless incomplete, overview of the long-term effects of SDB on cardiovascular autonomic function in humans, focusing directly on the knowledge derived from continuous measurements of heart rate, blood pressure and respiration obtained noninvasively during wakefulness and sleep. The rapid development of new and low-cost wearable technologies presages the need for smarter utilization and improved methods for interpreting the ever-increasing amounts of physiological data being collected by these devices. Conventional univariate analyses of heart rate, blood pressure and respiratory variability provide useful information about cardiovascular autonomic control. However, a multivariate model-based approach, by elucidating the causal, dynamic interrelationships among these measurements, gives us the ability to interpret the data on a more contextual basis and thus make inferences that are more accurate and relevant to autonomic health.

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KEY POINTS

- A large body of evidence suggests that abnormal autonomic control is an important causal link between sleep-disordered breathing (SDB) and cardiovascular disease.
- Heart rate variability and peripheral arterial tonometry have been employed to detect and assess autonomic changes in SDB, but the mechanistic information derived from these techniques is limited by the univariate nature of the underlying analyses.
- An alternative approach is to employ multivariate dynamic models that enable the causal dependencies among respiration, blood pressure, heart rate variability and peripheral vascular resistance to be quantified, and from which compact descriptors (“biophysical markers”) are derived.
- The model-derived markers representing respiratory-cardiac coupling, baroreflex control of heart rate, and blood pressure modulation of peripheral vascular resistance are significantly altered in patients with SDB during wakefulness and sleep.

Figure 1.

Schematic block diagram of the closed-loop minimal model of heart rate and blood pressure variability. Fluctuations in R-R interval (RRI) result from respiratory-cardiac coupling (RCC) and a component mediated through the arterial baroreflexes (ABR). Other factors are represented as "extraneous influences on RRI". These components account for the "forward" part of the model that generates heart rate variability (rectangular block with broken lines). The "other half" of the closed-loop model consists of the components responsible for generating blood pressure variability: fluctuations in cardiac output (from heart rate and stroke volume changes), fluctuations in systemic vascular resistance, and respiration,

Figure 2. Effects of sleep-disordered breathing and sleep-wake state on the estimated impulse response magnitudes of the RCC (left panel) and ABR (right panel) components of the model. Adapted from: Jo et al., *Am J Physiol Heart Circ Physiol* 288: H1103–H1112, 2005.

Figure 3. (Left) Data collected from a subject during spontaneous breathing. “BP” represents beat-averaged arterial blood pressure, “ ΔV ” is change in lung volume (respiration), and “PATamp” is the beat-to-beat amplitude of the peripheral arterial tonometer signal. “BP” and “ ΔV ” are considered the inputs, and “PATamp”, taken to represent the change in peripheral vascular conductance (ΔG_{pV}), is treated as the output. (Right) The linear and nonlinear components of the model (see Equation 4) are estimated from these data.

Figure 4.

Autonomic reactivity to orthostatic stress in obese adolescents with sleep-disordered breathing (SDB) and insulin resistance versus obese adolescent controls. The model-derived marker shown here is the magnitude of the blood pressure to peripheral vascular conductance nonlinear kernel. BPC nonlinear gain decreased significantly more in SDB subjects compared to controls following change in posture from supine to standing. Lines connect the supine and standing values of each individual. Closed circles and error bars represent group means and standard errors of the parameter estimates.