Model-Derived Markers of Autonomic Cardiovascular Dysfunction in Sleep-Disordered Breathing

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KEYWORDS

• Heart rate variability • Cardiorespiratory control • Minimal model • Sleep apnea
• Peripheral vascular resistance

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 used 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 use 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.

INTRODUCTION AND BACKGROUND

Several large epidemiologic 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 more than 700 subjects, demonstrated that the adjusted odds ratio of incident systemic hypertension in SDB subjects with respiratory disturbance index greater than 15 was almost 3 times higher relative to subjects without SDB.[3] In the Sleep Heart Health Study cohort of 6132 subjects, SDB was found to be strongly correlated with coronary heart disease, heart failure, and stroke.[4] Nieto and colleagues[5] found the odds ratio of hypertension to increase with severity of SDB. Studies using 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 and colleagues[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 carryover effect in the daytime. In a rat model, Fletcher and colleagues[8,9] found that sustained hypertension developed after a few weeks

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Sleep Med Clin 11 (2016) 489–501
http://dx.doi.org/10.1016/j.jsmc.2016.07.003

of exposure to intermittent hypoxia without any accompanying upper airway obstruction.

There are several 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 using 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 and colleagues[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 and colleagues[19] found that exposing healthy young subjects to intermittent asphyxia over a period of 20 minutes led to sympathetic activation that continued even after the stimulus was removed. In another study, prolonged sympathetic activation was produced after 20 minutes of 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 postrecovery 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 colleagues[24] found abnormal baroreflex sympathetic modulation in subjects with SDB. The authors' 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" VERSUS "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 because 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 nonintrusiveness of obtaining the measurements on a continuous basis over significant lengths of time, including during sleep, because 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 RR 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 pharmacologic interventions were used 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 using 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 physiologic mechanisms. One way of overcoming the limitations inherent in univariate signal analysis