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Sleep and Cardiovascular Disease: An Overview

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Considerable progress has been made regarding the interactions between sleep and cardiovascular diseases[1–3]. Historically, a number of abnormalities have been linked with sleep apnea but are likely a reflection of the comorbidities associated with morbid obesity rather than causal[4]. More recently, however, certain sleep disorders have been proven to cause cardiovascular disease; e.g., obstructive sleep apnea has now been definitively proven to cause systemic hypertension[5–10] and possibly myocardial infarction[11], congestive heart failure,[12] stroke[13,14] and death[15–18]. In addition, cardiovascular diseases can disrupt sleep, as is the case in congestive heart failure patients who experience paroxysmal nocturnal dyspnea from Cheyne Stokes breathing[19]. As is discussed in this issue of *PCD*, the science is rapidly evolving regarding our understanding of the mechanisms underlying and linking these phenomena.

Sleep deprivation is exceedingly common in modern society with compelling data suggesting progressive reductions in sleep duration for North Americans over the past several decades. In some series, only 3% of children were actually acquiring the recommended 9 hours of sleep per night[20]. Although the neurocognitive consequences of sleep deprivation are well known and well established[21,22], emerging data suggest major metabolic[23–25] and cardiovascular consequences to chronic partial sleep restriction[26]. As discussed in this issue of *PCD*, sleep deprivation in physiological studies can induce impairments in insulin sensitivity[27] and hormonal changes that can mediate increases in hunger and appetite[25]. Indeed epidemiological studies have also shown increases in body weight in short sleepers as compared with those who sleep 7–8 hours per night, although the precise mechanisms remain unclear[24]. Some data also suggest that short sleepers have an increased incidence of myocardial infarction[26] and all cause mortality[28] as compared with conventional sleepers, independent of known confounding variables. Interestingly, long sleepers (>9 hours per night) also appear to have an excess risk of complications[29]. The epidemic of chronic partial sleep restriction is likely to become recognized as a public health problem owing to the severe complications that are increasingly appreciated. Public education of the health effects of sleep deprivation should be a priority.

Obstructive sleep apnea is a highly prevalent condition with well established neurocognitive and cardiovascular sequelae[1]. Although 4% of North American middle aged men and 2% of North American women have symptomatic sleep apnea according to a frequently cited 1993 paper[30], these figures likely represent underestimates. Since 1993, the prevalence of obesity has increased considerably[31–33], the technology has improved to detect more subtle respiratory events[34], and the data have evolved such that limiting the definition of OSA based on symptoms of sleepiness is likely inappropriate. Because of the numerous associated comorbidities, the proof of apnea-attributable complications has been challenging. Three lines of investigation

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have led to this proof of causation: mechanistic animal studies, large well controlled human epidemiological studies, and human interventional studies. First, using elegant animal models, Brooks *et al*. demonstrated that the induction of sleep apnea in the tracheostomized dog led to elevations of systemic blood pressure, which were then reversible with the elimination of apnea[10]. Second, in large scale human epidemiological studies, obstructive sleep apnea has an increased prevalence as well as incidence of systemic hypertension, independent of known confounders[7,9]. A dose-response relationship of increasing risk of hypertension with increasing severity of sleep apnea has been observed. Longitudinal analyses have shown a tripling of risk of incident hypertension over the course of 4 years among moderate OSA patients as compared with carefully matched controls[7]. The apnea-hypopnea index, a common metric of sleep apnea severity, has greater predictive value for hypertension than does body mass index in some studies[5]. Third, interventional studies using nasal continuous positive airway pressure have demonstrated improvement in hypertension with treatment of OSA[35]. Although the magnitude of the effect is quite variable across different studies, the bulk of the evidence suggests important improvements in blood pressure with sleep apnea therapy[36]. Nocturnal surges in blood pressure, which may provide a substrate for plaque rupture, are known to occur during obstructive apnea[37]. However, these intermittent surges in blood pressure and the impact of their elimination have been less carefully studied in the OSA arena. Patients with drug refractory hypertension also have marked improvements in blood pressure with sleep apnea therapy in some small studies[38,39]. Thus, although further work is required, OSA now has a proven causal effect on systemic blood pressure elevation.

Regarding potential mechanisms, a number of issues are addressed in this issue of *PCD*. Autonomic factors are likely important[3,40,41], but newer data suggest important roles for inflammatory factors, oxidative stress, and metabolic factors, among others. Acute hemodynamic alterations in OSA result from sustained breathing efforts during pharyngeal collapse yielding markedly negative intrathoracic pressure, hypoxemia, and arousal from sleep[1,2]. Negative intrathoracic pressure increases transmural cardiac pressure, effectively increasing ventricular wall tension and afterload[42]. In addition, augmented venous return and increased pulmonary arterial pressures from hypoxemia may elevate right ventricular pressures, resulting in a leftward shift of the inter-ventricular septum[43,44]. The concomitant hypoxemia and arousals from sleep lead to sympathetic surges augmenting blood pressure and heart rate. Thus, each episode of obstructive apnea may yield impaired left ventricular filling, elevated ventricular afterload, and increased myocardial oxygen demand in patients with hypoxemia[45]. Institution of CPAP (continuous positive airway pressure) decreases left ventricular afterload and venous return, and minimizes hypoxemia and sympathoexcitation[46].

As detailed in this *PCD*, recurrent hypoxemia followed by reoxygenation resembles ischemia reperfusion events, and the re-oxygenation phase yields reactive oxygen species[47]. Endothelial cells are particularly vulnerable to oxidative stress, since reactive oxygen species decrease NO production and may inactivate bioavailable NO, thus reducing the protective effect of endothelium-derived NO[48,49]. Intermittent hypoxemia also activates NF-κB producing a pro-inflammatory environment, potentially promoting atherosclerosis[50]. Indeed, the degree of hypoxemia predicts the degree of endothelial dysfunction in OSA[51].

OSA has been linked to congestive heart failure, stroke, atrial fibrillation, and myocardial infarction in some cross- sectional studies[12,52,53]. Recent longitudinal studies suggest an important incidence of stroke in OSA independent of known confounding variables[13,14,54]. Although long term follow up studies have suggested reduced risk of fatal and non-fatal cardiovascular events in OSA patients treated with CPAP as compared with untreated patients, such studies are complicated to interpret[55,56]. Presumably, the CPAP-adherent patients are highly motivated, well educated people who are more likely to take their medications or call

their physician in case of problems; i.e., such studies are susceptible to the healthy participant bias[57]. Thus, randomized trials will be required to draw any definitive conclusions. Such trials are difficult to design both logistically and ethically as discussed in this *PCD*. Because of the known symptomatic benefits of CPAP, many practioners are reluctant to withhold CPAP from afflicted patients for long periods of time awaiting vascular events in the context of a clinical trial. By contrast, asymptomatic OSA patients are unlikely to be adherent with CPAP in the long term[58,59], making a definitive study difficult to design.

With regard to congestive heart failure, the situation is quite complicated. Patients with congestive heart failure frequently have abnormalities observed during sleep recordings[60,61]. Roughly one-third of CHF patients with left ventricular dysfunction will have evidence of obstructive sleep apnea, while another third will have evidence of Cheyne Stokes respirations (CSR, a form of central apnea)[60]. In some studies, the overall prevalence of sleep disordered breathing is 50%, with a predominance of CSR over OSA[61]. In many cases, the distinction between OSA and CSR is difficult to make in congestive heart failure, leading some investigators to suggest the term, “sleep disordered breathing (SDB),” should be used to describe both forms of breathing abnormality[62]. Breathing abnormalities are also quite common during the sleep of patients with diastolic heart failure[63]. Although the prevalence of SDB in CHF is quite high, the importance of this condition remains controversial[64–67]. While some data suggest an important attributable mortality to CSR in CHF, other data suggest no major association. Thus, further study is clearly required.

A number of points deserve emphasis about sleep disordered breathing in CHF. First, optimization of medical therapy is a cornerstone of treatment[68], as a number of studies have shown resolution of CSR with adequate dosing of cardiac medications. Second, positive airway pressure has a number of hemodynamic influences, including reductions in cardiac preload and cardiac afterload[42,45,69], improvements in oxygenation, suppression of catecholamine release, and improvements in left ventricular function[70–72]. Third, the data regarding CPAP therapy for SDB in CHF are equivocal[73]. In OSA, the existing studies are quite small but do suggest some improvement in left ventricular ejection fraction with CPAP[74,75]. In CSR, the largest study showed no improvement in transplant-free survival in CHF patients with CSR treated with CPAP as compared with medically treated controls[73]. Thus, CPAP cannot currently be recommended for CSR. Fourth, newer devices are under development to stabilize breathing acutely during sleep[19,76,77]; however, outcome data are currently lacking for these newer devices. Fifth, cardiac resynchronization therapy has been shown to improve both central and obstructive apnea, although the magnitude of the benefit is somewhat variable[78,79]. Thus, OSA and CSR are highly prevalent in CHF, although the approach to management beyond optimization of medical therapy remains unclear.

In summary, sleep is an evolving discipline making some exciting contributions to the cardiovascular literature. Compelling data reveal important effects of sleep deprivation, obstructive sleep apnea, and Cheyne Stoke respirations on cardiovascular and metabolic health. Despite these compelling data, however, sleep issues have not been embraced by the cardiology community (see Table 1). For the clinician, an appreciation for the importance of these conditions is now required to provide optimal patient care. For the clinical researcher, a number of interventional studies need to be performed to determine how best to reduce the risk caused by various sleep disorders. For the basic scientist, as reviewed in this *PCD*, we are just beginning to understand the mechanisms underlying the various cardiovascular manifestations of sleep disturbances. For the epidemiologist, the public health impact of sleep apnea (partially as a result of the obesity pandemic) and chronic partial sleep deprivation needs to be become general knowledge. For junior faculty and trainees, the sleep field represents a major opportunity as the discipline is in serious need of talented young investigators and clinicians. Clearly, we all have work to do.

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Table I

Potential Reasons that Sleep Issues Have Not Been Embraced by The Cardiology Community

	Concern	Response	Potential Solution
Clinician Factors	Lack of awareness by physicians	Traditionally no teaching in medical school and residency	Enhanced medical education
	Lack of classic symptoms such as sleepiness in CHF[80]	Routine, thorough questioning in medical history	High index of suspicion
	Concerns about confounding of OSA by covariates, such as obesity in prior studies[4]	Large, rigorous studies have now shown independent effects of OSA[7]	Interventional studies help to show treatment of sleep apnea *per se* is important[35]
	Lack of mechanistic research, particularly for sleep deprivation	Data are evolving; field is young	Further research
	Lack of definitive multicenter RCTs	-Ethical barriers to withholding therapy insymptomatic OSA patients. -Poor adherence and potential lack of efficacy in asymptomatic OSA patients	-Further research -Develop better treatments -Large scale studies
Patient Factors	Lack of awareness by patients	Traditionally lack of importance placed on sleep duration and symptoms of sleep disorders	-Public education -Lay press
	Reluctance to undergo diagnostic testing	Sleep study is innocuous compared to many diagnostic tests in cardiology	-Patient education -Development of newer technologies to diagnose sleep disorders in the home.
	Reluctance to use CPAP or other positive airway pressure devices	-Some patients feel much better. -Adherence is comparable to other chronic medical therapies[81]. -Bed partner is often happy with alleviation of snoring. -Newer technologies with blowers, masks, and humidifiers are available.	-Develop better technologies -Provide more definitive data -Patient education -Intensive support[82]