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# Sleep apnea and the heart

## ■ ABSTRACT

The normal sleep-wake cycle is characterized by diurnal variations in blood pressure, heart rate, and cardiac events. Sleep apnea disrupts the normal sleep-heart interaction, and the pathophysiology varies for obstructive sleep apnea (OSA) and central sleep apnea (CSA). Associations exist between sleep-disordered breathing (which encompasses both OSA and CSA) and heart failure, atrial fibrillation, stroke, coronary artery disease, and cardiovascular mortality. Treatment options include positive airway pressure as well as adaptive servo-ventilation and phrenic nerve stimulation for CSA. Treatment improves blood pressure, quality of life, and sleepiness, the last particularly in those at risk for cardiovascular disease. Results from clinical trials are not definitive in terms of hard cardiovascular outcomes.

## ■ KEY POINTS

Diurnal variations in blood pressure, heart rate, and cardiac events occur during normal sleep.

While normal sleep may be cardioprotective, sleep apnea disrupts the normal sleep-heart interaction.

Untreated severe sleep apnea increases the risk for cardiovascular events.

Treatment with continuous positive airway pressure (CPAP) may reduce the risk of cardiac events based on some data, though randomized studies suggest no improvement in cardiovascular mortality.

Poor patient adherence to CPAP makes it difficult to evaluate the efficacy of CPAP treatment in clinical trials.

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## ■ SLEEP AND CARDIOVASCULAR PHYSIOLOGY

Wakefulness and sleep, the latter comprised of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, comprise our primary states of being. Sleep states oscillate between NREM and REM sleep. The first and shortest period of REM sleep typically occurs 90 to 120 minutes into the sleep cycle. Most REM sleep, including the longest period of REM sleep, occurs during the latter part of the sleep cycle.

With these sleep state changes, physiologic changes also occur, such as reduced heart rate and blood pressure because of enhanced parasympathetic tone. During REM sleep, there are also intermittent sympathetic nervous system surges. Other physiologic changes include a regular respiratory rate during NREM sleep and an irregular respiratory rate during REM sleep. Body temperature is normal during NREM sleep and poikilothermic (ie, tends to fluctuate) during REM sleep. Blood pressure is reduced 10% to 15% during sleep<sup>1</sup> and then rises, so that the highest blood pressure occurs in the morning. Data from 10 million users of activity-monitoring devices show that the heart rate changes during sleep.<sup>2</sup> The heart rate is decreased in those who get less than 7 hours of sleep, then increases with longer sleep duration in a U-shaped distribution.

Cardiovascular events are more likely to occur at certain times of day. Myocardial infarction is more likely in the morning, with a threefold increased risk within the first 3 hours of awakening that peaks around 9 AM.<sup>3,4</sup> Similar diurnal patterns have been observed with other cardiovascular conditions such as sudden cardiac death and ischemic episodes, with the highest risk during morning hours (6 to 9 AM).<sup>4</sup>

The reason for this morning predisposition for cardiovascular events is unclear, but it is thought that perhaps the autonomic fluctuations that occur during REM sleep and the predominance of REM sleep in early morning may be a factor. Diurnal changes in blood pressure and cortisol levels may also contribute, as well as levels of systemic inflammatory and thrombotic markers such as plasminogen activator inhibitor 1.

Arrhythmias are also more likely to occur in a diurnal pattern. Atrial fibrillation (AF), particularly paroxysmal AF, is believed to be vagally mediated in 10% to 25% of patients.<sup>5</sup> Therefore, for those who are predisposed, sleep may represent a period of increased risk for AF. In a study of individuals 60 years and older, the maximum duration and peak frequency of AF occurred from midnight to 2 AM.<sup>5</sup>

Recent studies have found that REM-related obstructive sleep apnea (OSA) is associated with increased cardiovascular risk. Experimental models show that REM sleep may increase the risk for compromised coronary blood flow.<sup>6</sup> Increased heart rate corresponds to reduced coronary blood flow and thus, to decreased coronary perfusion time and less time for relaxation of the heart, increasing the risk for coronary artery disease, thrombosis, and ischemia.

## ■ SLEEP APNEA PATHOPHYSIOLOGY

The normal physiology of the sleep-heart interaction is disrupted by sleep apnea. OSA is defined as episodes of complete or partial airway obstruction that occur during sleep with thoracoabdominal effort. Central sleep apnea (CSA) is the cessation of breathing with no thoracoabdominal effort. The pathophysiology of the sleep-heart interaction varies for OSA and CSA.

**Diurnal variations in blood pressure, heart rate, and cardiac events occur during normal sleep.**

### Obstructive sleep apnea

OSA is a nocturnal physiologic stressor that is highly prevalent and underrecognized. It affects approximately 17% of the adult population, and the prevalence is increasing with the obesity epidemic. Nearly 1 in 15 individuals is estimated to be affected by at least moderate OSA.<sup>7,8</sup> OSA is underdiagnosed particularly in minority populations.<sup>9</sup> Data from the 2015 Multi-Ethnic Study of Atherosclerosis (MESA) showed undiagnosed moderate to severe sleep apnea in 84% to 93% of individuals,<sup>9</sup> similar to an estimated 85% of undiagnosed cases in 2002.<sup>10</sup>

OSA is highly prevalent in individuals with underlying coronary disease<sup>11–13</sup> and in those with cardiovascular risk factors such as diabetes, hypertension, and heart failure. The prevalence of OSA in patients with cardiovascular disease ranges from 30% (hypertension) to 60% (stroke or transient ischemic attack, arrhythmia, end-stage renal disease).<sup>14</sup>

### Pathophysiology of OSA

The pathophysiology of OSA can be observed during polysomnography, characterized by autonomic nervous system disturbances, intermittent hypoxia, and intra-

thoracic pressure alterations, (Figure 1). Intermittent bouts of hypoxia or oxygen-lowering occur because airflow is obstructed despite persistent thoracic and abdominal effort. Systemic inflammation and oxidative stress occur due to these intrathoracic pressure alterations, increased CO<sub>2</sub> and reduced oxygen levels, and autonomic nervous system disturbances.

The alterations in sympathetic activation that occur during sleep in patients with OSA persist during wakefulness. Microneurographic recording of sympathetic nerve activity in the peroneal nerve reveal that the rate of sympathetic bursts doubles and the amplitude is greater in individuals with OSA compared with a control group.<sup>15</sup>

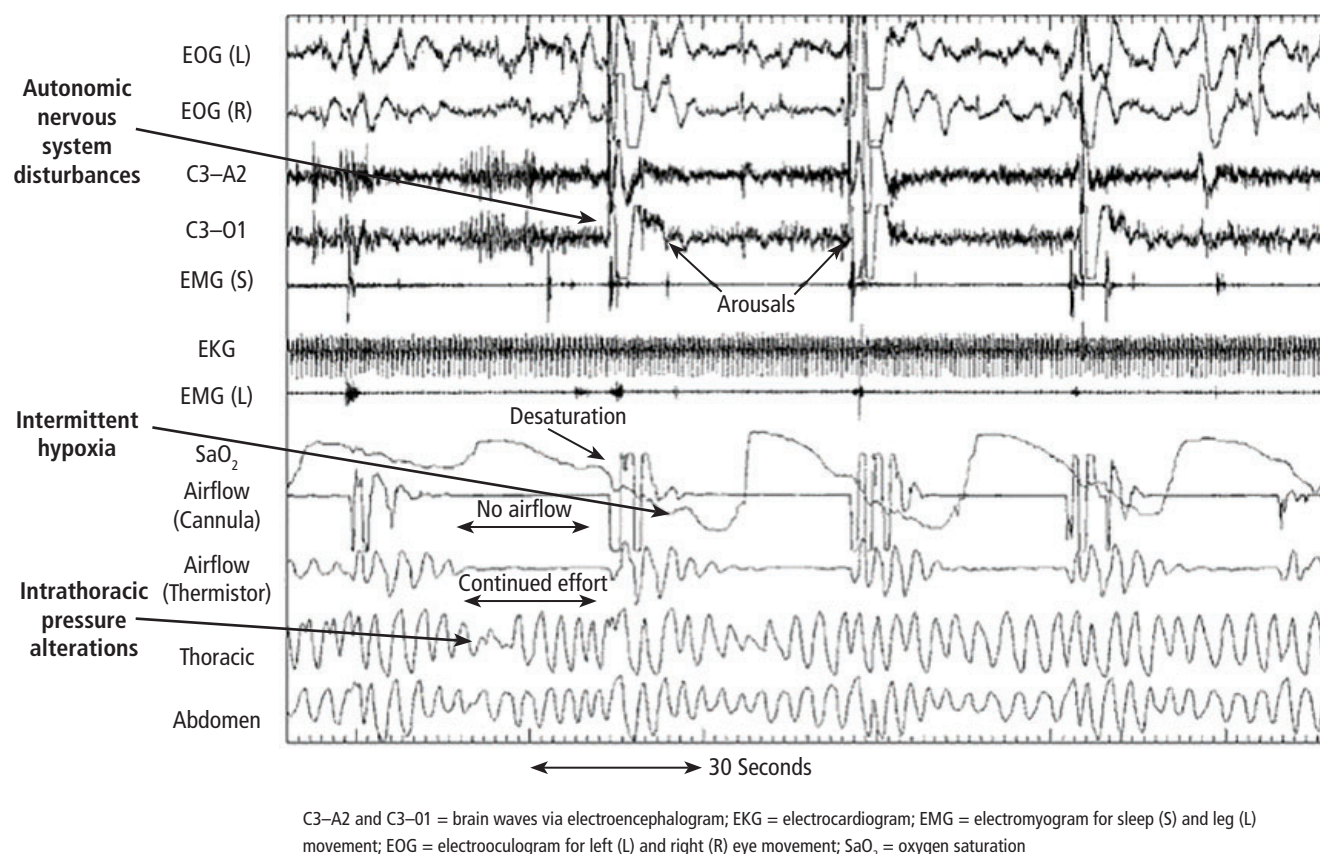
Sympathetic nerve activity, blood pressure, and heart rate were shown to increase during REM sleep in individuals with OSA on continuous positive airway pressure (CPAP) during an induced apneic event (pressure reduction from 8 cm to 6 cm of water).<sup>15</sup>

During OSA episodes, there is an increased cardiac load. Impaired diastolic function and atrial and aortic enlargement, and in particular, the thin-walled atria are very susceptible to the intrathoracic pressure swings caused by OSA. Physiologic changes with OSA from pressure changes in the chest result in shift of the intraventricular septum, causing a reduction in cardiac output.<sup>16</sup> With the lowering of oxygen during episodes of apnea, constriction of the pulmonary vasculature leads to elevation of pressure in the pulmonary vasculature reflected by the increase in mean pulmonary arterial pressures.<sup>17</sup>

Other studies have shown that OSA increases upregulation of markers of systemic inflammation and prothrombotic markers, the very markers that can increase cardiovascular or atherogenic risk.<sup>18–22</sup> One example is the soluble interleukin 6 receptor, shown to be elevated in the morning relative to sleep apnea compared with the evening.<sup>20</sup> Other biomarkers observed to be associated with sleep apnea include markers of prothrombotic potentials such as plasminogen activator inhibitor 1.<sup>19</sup> Oxidative stress occurs because intermittent bouts of lower oxygen can lead to oxidation of serum proteins and lipids. Endothelial dysfunction has been observed as well as insulin resistance and dyslipidemia.<sup>23</sup> Taken together, these are pathways that lead to atherogenesis and increased cardiovascular risk.

### Central sleep apnea

CSA episodes are the cessation of breathing without thoracoabdominal effort, in contrast to the persis-



**Figure 1.** A polysomnogram showing autonomic nervous system disturbances, intermittent hypoxia, and intrathoracic pressure alterations.

tence of thoracoabdominal effort in OSA. CSA is characterized by breathing instability with highly sensitive chemoresponses and prolonged circulation time.<sup>24</sup> This can be physiologic in some cases, as when it occurs after a very large breath or sigh and then a central apnea event occurs after the sigh. The alterations in oxygen and CO<sub>2</sub> and the stretch of the receptors in the alveoli of the lungs initiate the Hering-Breuer inhalation reflex.

## Pathophysiology of CSA

Complex pathways of medullary and aortic receptor chemosensitivity are at the root of the pathophysiology of CSA.<sup>24</sup> With CSA there is often a relative state of hypocapnia at baseline. During sleep, there is reduction in drive, thus chemosensitivity can be activated so that central apnea episodes can ensue as a result of alterations in CO<sub>2</sub> (ie, hypocapnia). Another factor that can contribute to the pathophysiology of CSA is arousal from sleep that can reduce CO<sub>2</sub> levels and therefore perpetuate central events.

The concept of loop gain is used to understand

the pathophysiology of CSA. Loop gain is a measure of the relative stability of a ventilation system and indicates the likelihood of an individual to have periodic breathing. It is calculated by the response to a disturbance divided by the disturbance itself.<sup>25</sup> With a high loop gain, there is a more pronounced or exuberant response to the disturbance, indicating more instability in the system and increasing the tendency for irregular breathing and CSA episodes.

Hunter-Cheyne-Stokes respiration occurs with CSA and is characterized by cyclical crescendo-decrescendo respiratory effort that occurs during wakefulness and sleep without upper-airway obstruction.<sup>26,27</sup> Unlike OSA, which is worse during REM sleep, Hunter-Cheyne-Stokes breathing in CSA is typically worse in NREM sleep, during N1 and N2 in particular.

## SLEEP APNEA AND HEART FAILURE

Both OSA and CSA are prevalent in patients with heart failure and may be associated with the progression of heart failure. CSA often occurs in patients with heart failure. The pathophysiology is multi-



factorial, including pulmonary congestion that results in stretch of the J receptors in the alveoli, prolonged circulation time, and increased chemosensitivity.

Complex pathways in the neuroaxis or somnogenic biomarkers of inflammation or both may be implicated in the paradoxical lack of subjective sleepiness in the presence of increased objective measures of sleepiness in systolic heart failure. One study found a relationship with one biomarker of inflammation and oxidative stress as it relates to objective symptoms of sleepiness but not subjective symptoms of sleepiness.<sup>28</sup>

Another contributing factor in the relationship between OSA and CSA in heart failure has also been described related to rostral shifts in fluid to the neck and to the pulmonary receptors in the alveoli of the lungs.<sup>29</sup> These rostral shifts in fluids may contribute to sleep apnea with parapharyngeal edema leading to OSA and pulmonary congestion leading to CSA.

Sleep apnea is associated with increased post-discharge mortality and hospitalization readmissions in the setting of acute heart failure.<sup>30</sup> Mortality analysis of 1,096 patients admitted for decompensated heart failure found CSA and OSA were independently associated with mortality in patients compared with patients with no or minimal sleep-disordered breathing.<sup>30</sup>

CSA has also been shown to be a predictor of readmission in patients admitted for heart failure exacerbations.<sup>31</sup> Targeting underlying CSA may reduce readmissions in those admitted with acute decompensated heart failure. While men were identified to be at increased risk of death relative to sleep-disordered breathing based on the initial results of the Sleep Heart Health Study, a subsequent epidemiologic substudy reflective of an older age group showed that OSA was more strongly associated with left ventricular mass index, risk of heart failure, or death in women compared with men.<sup>32</sup>

## Treatment

Standard therapy for treatment of OSA is CPAP. Adaptive servo-ventilation (ASV) and transvenous phrenic nerve stimulation are also available as treatment options in certain cases of CSA.

One of the first randomized controlled trials designed to assess the impact of CSA treatment on survival in patients with heart failure initially favored the control group then later the CPAP group and was terminated early based on stopping rules.<sup>33,34</sup> While adherence to therapy was suboptimal at an average of 3.6 hours, post hoc analysis showed that patients with CSA using CPAP with effective suppression of

CSA had improved survival compared with patients who did not have effective suppression using CPAP.<sup>34</sup>

ASV is mainly used for treatment of CSA. In ASV, positive airway pressure for ventilation support is provided and adjusts as apneic episodes are detected during sleep. The support provided adapts to the physiology of the patient and can deliver breaths and utilize anticyclic modes of ventilation to address crescendo-decrescendo breathing patterns observed in Hunter-Cheyne-Stokes respiration.

In the Treatment of Sleep-Disordered Breathing With Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients With Heart Failure (SERVE-HF) trial, 1,300 patients with systolic heart failure and predominantly CSA were randomized to receive ASV vs solely standard medical management.<sup>35</sup> The primary composite end point included all-cause mortality or unplanned admission or hospitalization for heart failure. No difference was found in the primary end point between the ASV and the control group; however, there was an unanticipated negative impact of ASV on cardiovascular outcomes in some secondary end points. Based on the secondary outcome of cardiovascular-specific mortality, clinicians were advised that ASV was contraindicated for the treatment of CSA in patients with symptomatic heart failure with a left ventricular ejection fraction less than 45%. The interpretation of this study was complicated by several methodologic limitations.<sup>36</sup>

The Cardiovascular Improvements With Minute Ventilation-Targeted Adaptive Servo-Ventilation Therapy in Heart Failure (CAT-HF) randomized controlled trial also evaluated ASV compared with standard medical management in 126 patients with heart failure.<sup>37</sup> This trial was terminated early because of the results of the SERVE-HF trial. Compliance with therapy was suboptimal at an average of 2.7 hours per day. The composite end point did not differ between the 2 groups; however, this was likely because the study was underpowered and was terminated early. Subgroup analysis revealed that patients with heart failure with preserved ejection fraction may benefit from ASV; however, additional studies are needed to confirm these findings.

Therefore, although ASV is not indicated when there is predominantly CSA in patients with systolic heart failure, preliminary results support potential benefit in patients with OSA and preserved ejection fraction.

Another novel treatment for CSA is transvenous phrenic nerve stimulation. A device is implanted that stimulates the phrenic nerve to initiate breaths.

The initial study of transvenous phrenic nerve stimulation reported a significant reduction in the number of episodes of central apnea per hour of sleep.<sup>38,39</sup> The apnea–hypopnea index improved overall and some types of obstructive apneic events were reduced with transvenous phrenic nerve stimulation.

A multicenter randomized control trial of transvenous phrenic nerve stimulation found improvement in several sleep apnea indices, including central apnea, hypoxia, reduced arousals from sleep, and patient reported well-being.<sup>40</sup> Transvenous phrenic nerve stimulation holds promise as a novel therapy for central predominant sleep apnea not only in terms of improving the degree of central apnea and sleep-disordered breathing, but also in improving functional outcomes. Longitudinal and interventional trial data are needed to clarify the impact of transvenous phrenic nerve stimulation on long-term cardiac outcomes.

## ■ SLEEP APNEA AND ATRIAL FIBRILLATION AND STROKE

### Atrial fibrillation

AF is the most common sustained cardiac arrhythmia. The number of Americans with AF is projected to increase from 2.3 million to more than 10 million by the year 2050.<sup>41</sup> The increasing incidence and prevalence of AF is not fully explained by the aging population and established risk factors.<sup>42</sup> Unrecognized sleep apnea, estimated to exist in 85% or more of the population, may partially account for the increasing incidence of AF.<sup>43</sup>

There are 3 types of AF, which are thought to follow a continuum: paroxysmal AF is characterized by episodes that occur intermittently; persistent AF is characterized by episodes that last longer than 7 days; chronic or permanent AF is typically characterized by AF that is ongoing over many years.<sup>44</sup> As with sleep apnea, AF is often asymptomatic and is likely underdiagnosed.

Sleep apnea and AF share several risk factors. Obesity is a risk factor for both OSA and AF; however, a meta-analysis supported a stronger association of OSA and AF vs obesity and AF.<sup>45</sup> Increasing age is a risk factor for both OSA and AF.<sup>46,47</sup> Although white populations are at higher risk for AF, OSA is associated with a 58% increased risk of AF in African Americans.<sup>48</sup> Nocturnal hypoxia has been associated with increased risk of AF in Asians.<sup>49</sup>

In terms of pathophysiology of sleep apnea and cardiac arrhythmia, OSA increases inflammation,

intrathoracic pressures, and CO<sub>2</sub> levels. The increase in inflammation and oxidative stress is thought to alter the cardiac electrophysiology of the heart and contribute to structural remodeling of the heart that increases the risk of cardiac arrhythmia (**Figure 2**).<sup>50</sup>

Experimental data continue to accrue providing biologic plausibility of the relationship between sleep apnea and AF. OSA contributes to structural and electrical remodeling of the heart with evidence supporting increased fibrosis and electrical remodeling in patients with OSA compared with a control group.<sup>51</sup> Markers of structural remodeling, such as atrial size, electrical silence, and atrial voltage conduction velocity, are altered in OSA.<sup>50</sup>

Data from the Sleep Heart Health Study show very strong associations between atrial and ventricular cardiac arrhythmias and sleep apnea with two- to fivefold higher odds of arrhythmias in patients with severe OSA compared with controls even after accounting for confounding factors such as obesity.<sup>52</sup>

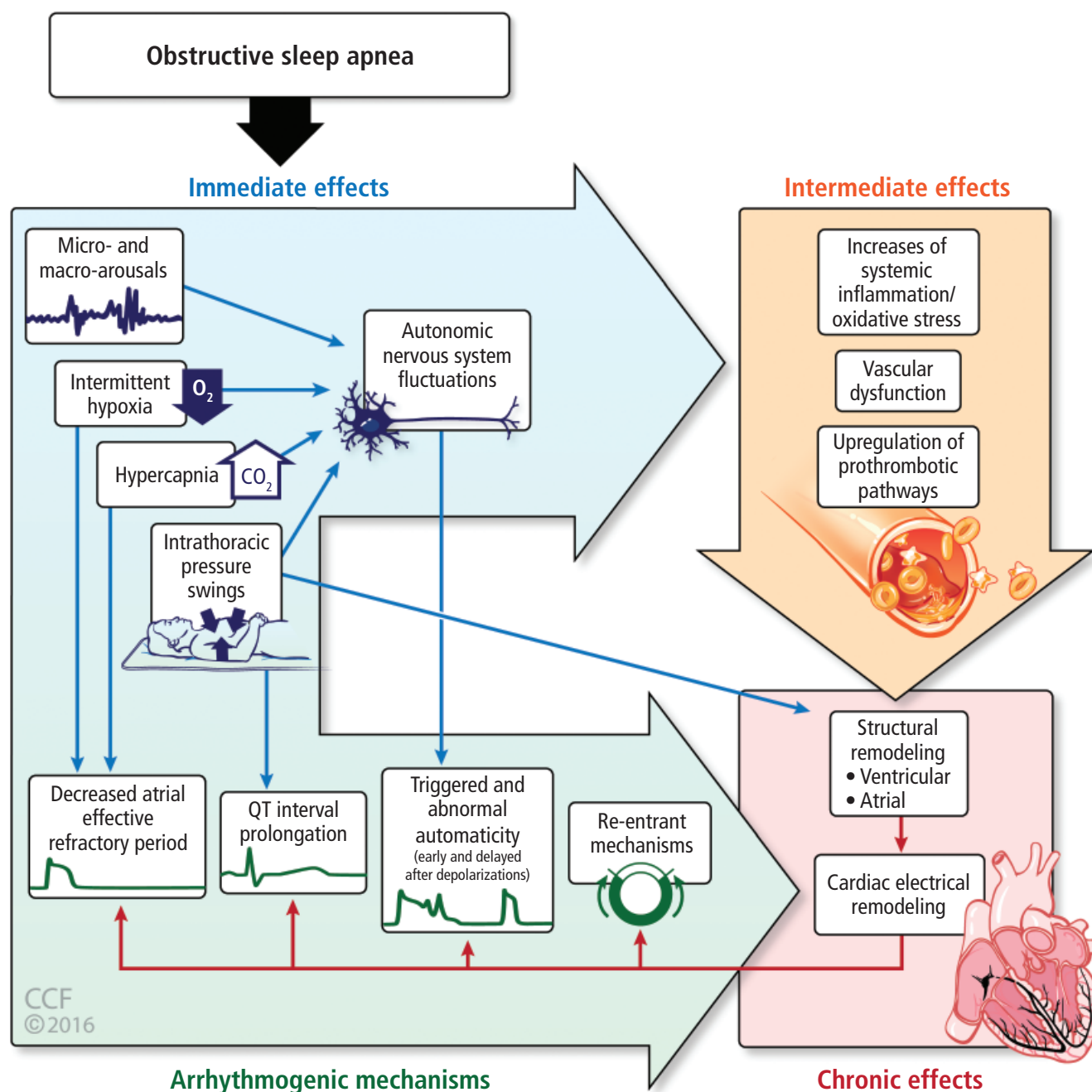
A multicenter, epidemiological study of older men showed that increasing severity of sleep apnea corresponds with an increased prevalence of AF and ventricular ectopy.<sup>53</sup> This graded dose-response relationship suggests a causal relationship between sleep apnea and AF and ventricular ectopy. There also appears to be an immediate influence of apneic events and hypopneic events as it relates to arrhythmia. A case-crossover study showed an associated 18-fold increased risk of nocturnal arrhythmia within 90 seconds of an apneic or hypopneic event.<sup>54</sup> This association was found with paroxysms of AF and with episodes of nonsustained ventricular tachycardia.

Data from a clinic-based cohort study show an association between AF and OSA.<sup>55</sup> Specifically, increased severity of sleep apnea was associated with an increased prevalence of AF. Increasing degree of hypoxia or oxygen-lowering was also associated with increased incidence of AF or newly identified AF identified over time.

Longitudinal examination of 2 epidemiologic studies, the Sleep Heart Health Study and Outcomes of Sleep Disorders Study in Older Men, found CSA to be predictive of AF with a two- to threefold higher odds of developing incident AF as it related to baseline CSA.<sup>56</sup> According to these data, CSA may pose a greater risk for development of AF than OSA.

With respect to AF after cardiac surgery, patients with sleep apnea and obesity appear to be at higher risk for developing AF as measured by the apnea–hypopnea index and oxygen desaturation index.<sup>57</sup>

Treatment of sleep apnea may improve arrhythm-



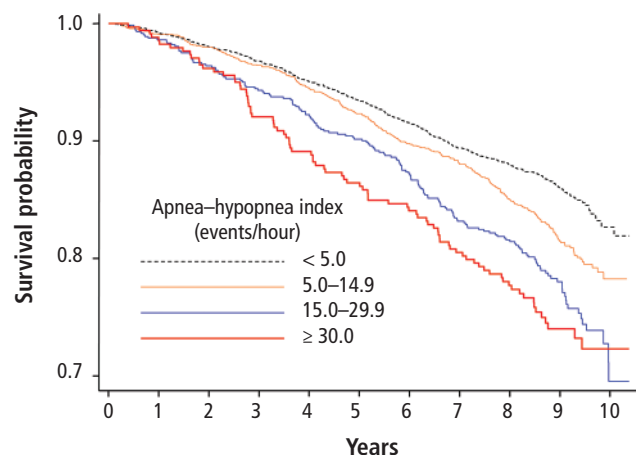
**Figure 2.** Pathophysiologic pathways of obstructive sleep apnea and cardiac arrhythmia.

mic burden. Case-based studies have shown reduced burden and resolution of baseline arrhythmia with CPAP treatment for OSA as therapeutic pressure was achieved.<sup>58</sup> Another case-based study involved an individual with snoring and OSA and AF at baseline.<sup>59</sup> Several retrospective studies have shown that treatment of OSA after ablation and after cardio-

version results in reduced recurrence of AF; however, large definitive clinical trials are lacking.

### Stroke

Sleep apnea is a risk factor for stroke due to intermittent hypoxia-mediated elevation of oxidative stress and systemic inflammation, hypercoagulability, and



Number  
at risk: 6,294 6,205 6,110 6,001 5,868 5,732 5,566 5,411 4,756 2,357 300  
Total  
deaths: 0 59 143 241 359 478 616 757 875 989 1,046

**Figure 3.** Survival of patients with obstructive sleep apnea by apnea-hypopnea index.

Punjabi NM, et al. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009; 6(8):e1000132.

impairment of cerebral autoregulation.<sup>60</sup> However, the relationship may be bidirectional in that stroke may be a risk factor for sleep apnea in the post-stroke period. The prevalence of sleep apnea post-stroke has been reported to be up to 70%. CSA can occur in up to 26% during the post-stroke phase.<sup>61</sup> Data are inconsistent in terms of the location and size of stroke and the risk of sleep apnea, though cerebrovascular neuronal damage to the brainstem and cortical areas are evident.<sup>62</sup> In one study, the incidence of stroke appeared to increase with the severity of sleep apnea.<sup>63</sup> These findings were more pronounced in men than in women; however, this study may not have captured the increased cardiovascular risk in postmenopausal women. The Outcomes of Sleep Disorders in Older Men study found that severe hypoxia increased the incidence of stroke, and that hypoxia may be a predictor of newly diagnosed stroke in older men.<sup>64</sup> Although definitive clinical trials are underway, post-hoc propensity-score matched analysis from the Sleep Apnea Cardiovascular Endpoints (SAVE) study showed a lower stroke risk in those adherent to CPAP compared with the control group (HR=0.56, 95% CI: 0.30-0.90).<sup>65</sup>

### ■ SLEEP APNEA, CORONARY ARTERY DISEASE, AND CARDIOVASCULAR MORTALITY

The association between sleep apnea and coronary artery disease and cardiovascular mortality was considered in a Spanish study of 1,500 patients followed for

**TABLE 1**

**Sudden death from cardiac causes by time of day**

	Proportion of patients with cardiac sudden death		
	With OSA (n = 78)	Without OSA (n = 34)	General population
Midnight to 5:59 AM	46	21	16
6 AM to 11:59 AM	20	41	30
Noon to 5:59 PM	9	26	29
6 PM to 11:59 PM	24	12	25

Data from reference 69.

10 years, which reported that CPAP therapy reduced cardiac events in patients with OSA.<sup>66</sup> Patients with sleep apnea had an increased risk of fatal myocardial infarction or stroke. Survival of patients treated for sleep apnea approached that of patients without OSA.

In a study of a racially diverse cohort, an association of physician diagnosed sleep apnea with cardiovascular events and survival was identified.<sup>67</sup> Diagnosed sleep apnea was estimated to confer a two- to three-fold increase in various cardiovascular outcomes and all-cause mortality.

All-cause mortality data from the Sleep Heart Health Study of more than 6,000 participants showed that progressive worsening of OSA as defined by the apnea-hypopnea index resulted in poorer survival even after accounting for confounding factors (Figure 3).<sup>68</sup> Decreased survival appeared to mostly affect men or patients under age 70.

The diurnal pattern of cardiovascular physiology as it relates to sleep is thought to be cardioprotective because of reductions in blood pressure and heart rate. However, in the case of OSA, there appears to be a nocturnal vulnerability or predilection for sudden cardiac death. Patients with OSA were shown to have a higher risk of sudden nocturnal cardiac death occurring from midnight to 6 AM compared with individuals without OSA and the general population (Table 1).<sup>69</sup>

The effect of treatment for sleep apnea on cardiovascular outcomes was the focus of a recent randomized controlled trial of nearly 3,000 participants with a mean follow-up of 4 years.<sup>65</sup> Use of CPAP compared with usual care found no difference in cardiovascular outcomes. However, secondary analysis revealed a possible benefit of a lower risk of stroke with use of CPAP therapy. Several factors should be considered in interpreting these findings: ie, low adherence



with CPAP therapy (3 hours), whether the study was sufficiently powered to detect a change in cardiovascular outcomes, and if the duration of follow-up was adequate. In terms of patient demographics and study generalizability, the study did not include patients with severe sleep apnea and hypoxia, and most participants were men, of Asian descent, with a mean body mass index of 28 kg/m<sup>2</sup>, and low levels of sleepiness at baseline.

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