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REVIEW

Sleep Apnea and Sudden Cardiac Death

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Sleep plays an integral role in maintaining health and quality of life. Obstructive sleep apnea (OSA) is a prevalent sleep disorder recognized as a risk factor for cardiovascular disease and arrhythmia. Sudden cardiac death (SCD) is a common and devastating event. Out-of-hospital SCD accounts for the majority of deaths from cardiac disease, which is the leading cause of death globally. A limited but emerging body of research has further elaborated on the link between OSA and SCD. In this article, we aim to provide a critical review of the existing evidence by addressing the following questions: (1) what epidemiologic evidence exists linking OSA to SCD; (2) what evidence exists for a pathophysiologic connection between OSA and SCD; (3) are there electrocardiographic markers of SCD found in patients with OSA; (4) does heart failure represent a major effect modifier regarding the relationship between OSA and SCD; and (5) what is the impact of sleep apnea treatment on SCD and cardiovascular outcomes. Finally, we elaborate on ongoing research to enhance our understanding of the OSA-SCD association.

Key Words: Obstructive sleep apnea; QTc; Sleep; Sudden cardiac death; Ventricular arrhythmia

Disorders of sleep such as obstructive sleep apnea (OSA), insomnia, abnormal sleep duration, and poor sleep quality have been associated with cardiovascular disease (CVD) morbidity and mortality.[1–5] OSA, despite being underdiagnosed, is by far the most common form of sleep apnea, affecting 9–38% of the global adult population.[6] Its prevalence increases with body weight, age, and being male.[6–8] Given the aging population and pandemic of obesity globally, the public burden of OSA is likely to increase further.[9–11] OSA's impact on CVD has been highlighted extensively, and the condition has been linked to increased risk of congestive heart failure (CHF), coronary artery disease (CAD), stroke, atrial fibrillation (AF), sinus pauses, increased burden of premature ventricular complexes (PVC), and first-degree heart block.[3,5,12–14]

Sudden cardiac death (SCD) is defined as an unanticipated natural death from cardiac pathology ≤1 h from symptom onset in a person without any prior condition that would appear fatal.[15] According to the American Heart Association, in the USA, approximately 366,807 cases of SCD occurred in 2015.[16] Globally, CVD is the leading cause of mortality, with SCD being the most common manifestation.[17] Fatal arrhythmia is widely recognized as the underlying process in the majority of cases of SCD, with ischemic heart disease present in 75% of cases.[18] A number of studies have examined the role OSA plays in malignant arrhythmias by characterizing its association with high-risk electrocardiography (ECG) features.[19–24] Despite the paucity of evidence, there is a growing body of work evaluating OSA as a risk factor for SCD. In the present study we lay out connections between SCD and OSA that have been highlighted in recent studies.

Methods

Based on the consensus of three reviewers, targeted areas of review were determined. Thereafter, all three reviewers independently searched Pubmed, Medline US, NIH Clinicaltrial.gov, and Google Scholar to find studies pertinent to the targeted questions. We restricted our search to manuscripts published in peer-reviewed journals from 1980 to 2018. The primary search phrases used were "obstructive sleep apnea", "sudden cardiac death", "ventricular arrhythmia", "arrhythmia", "atrial fibrillation", "cardiac arrest", "arrhythmogenic", "continuous positive airway pressure", "sleep disordered breathing", "coronary artery disease", "acute coronary syndrome" "pathophysiology", "epidemiology", "prolonged QTc", "nocturnal sudden death", and "heart failure". Subsequently, other studies were identified based on the citations of the retrieved studies. A total of 79 articles were used for this review. Critical assessment for each article was independently performed by three reviewers.

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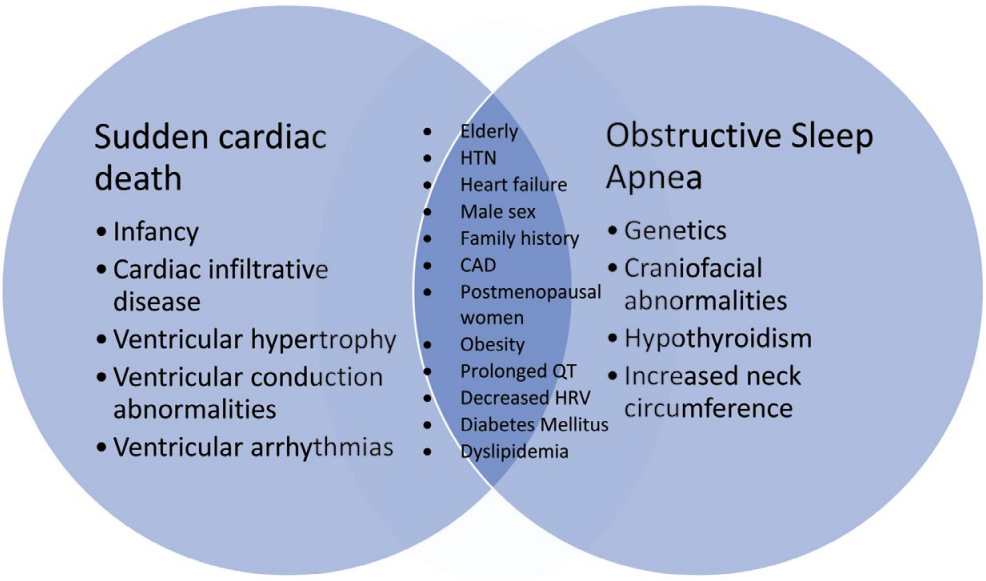

Figure 1. Shared risk factors between sudden cardiac death and obstructive sleep apnea. CAD, coronary artery disease; HRV, heart rate variability; HTN, hypertension.

Epidemiologic Evidence Linking OSA and SCD

There is a paucity of epidemiological data examining the association between OSA and SCD. This is largely attributed to the rarity of an adequately large cohort with availability of baseline information about OSA and a sufficient longitudinal follow-up period. Given that a sleep study is a prerequisite, it is impossible to derive any incident relationship in typical community-based cohorts that lack systematic OSA screening. This was overcome, however, in a clinic-based cohort study by Gami et al in which 10,701 adults who underwent clinically indicated sleep study in a single academic center were followed.[25] During an average 5-year follow-up, the investigators found that the lowest nocturnal O_2 saturation was independently, albeit modestly, predictive of SCD. Every 10% decrease in the lowest nadir O_2 saturation (cohort mean, 93±3%) was associated with a 14% increase in the risk of SCD. Despite statistical adjustments, these results could have been driven by underlying cardiopulmonary conditions or body habitus, which are associated with both nadir O_2 saturation and SCD.[26] More traditional metrics such as apnea-hypopnea index (AHI) were not predictive of SCD in the study. This study represents the first of its kind to implicate OSA as a possible independent risk factor for SCD.

A growing body of evidence has elaborated on the connection between OSA and various forms of CVD.[12,19–22] Individuals with OSA have a high burden of CVD, including CHF, which can serve as a substrate for SCD. Thus, CVD and its risk factors likely mediate the association between OSA and SCD. Research over the past two decades has identified many common risk factors shared by OSA and SCD that indirectly link the two entities (**Figure 1**).[7,17,18,27–29]

Impact of OSA on Nocturnal Sudden Death

Studies have brought to light a more specific link between OSA and SCD in the form of shifting day-night patterns of SCD in patient with OSA.[30,31] A 2005 retrospective study found that the relative risk of SCD was 2.57-fold higher between midnight and 6 a.m. in patients with OSA compared with the general population;[31] and, further, that this relative risk of SCD increased in proportion to the increasing severity of AHI.

Myocardial ischemia, a leading factor for SCD, is seen with a higher prevalence during nocturnal hours in patients with OSA.[32,33] A prior cohort study found that patients with OSA who had myocardial infarctions (MI) were 6-fold more likely to have the MI between the hours of midnight and 6 a.m. than those without OSA.[33] This change in the timing of MI may help explain, in part, the shifting day-night patterns of SCD in patients with OSA.

Even in the absence of CAD, nocturnal sudden death can still occur. The phenomenon of sudden unexplained nocturnal death in patients without known cardiac disease has been examined for more than a century.[34] Mutations in *SCN5A* that alter repolarization and predispose individuals to ventricular arrhythmia have become increasingly recognized as a contributing factor in nocturnal sudden death.[34,35] Patients with OSA are more likely to have nocturnal bradyarrhythmia than those without OSA,[36] and have a higher frequency of ventricular ectopy.[20,37] These electrophysiologic changes associated with OSA may contribute to nocturnal SCD in patients with channelopathies and altered repolarization.[34,35]

Common Pathophysiologic Connection Between OSA and SCD

OSA is characterized by repeated episodes of pharyngeal airway obstruction during sleep. This obstructed breathing leads to a cascade of responses by the body driven by swings in intrathoracic pressure and hypoxia (**Figure 2**). The resulting negative intrathoracic pressure increases

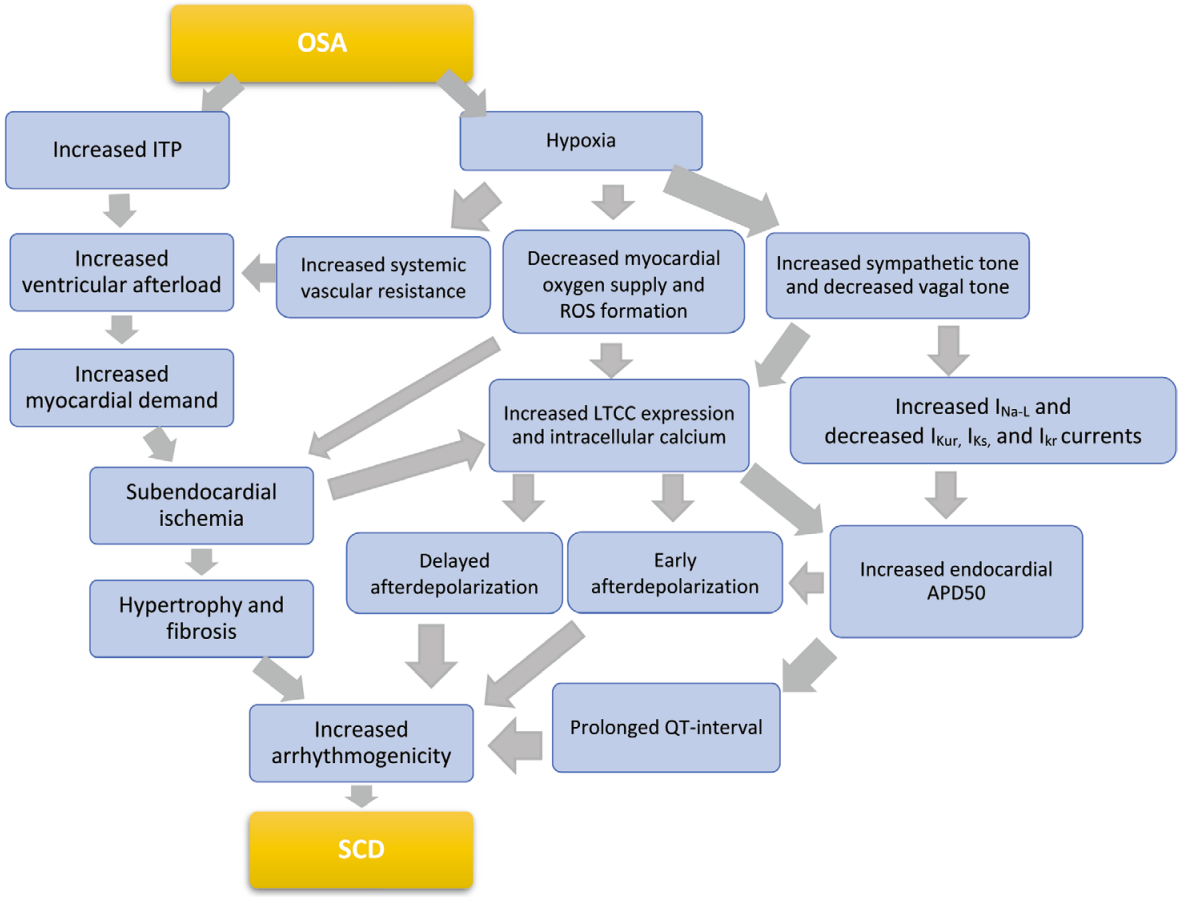

Figure 2. Proposed complex pathophysiology connecting obstructive sleep apnea (OSA) and sudden cardiac death (SCD). APD50, action potential duration 50%; I_{Kr}, rapid delayed rectifier current; I_{Ks}, slow delayed rectifier current; I_{Kur}, ultra rapid delayed rectifier current; $I_{Na\text{-}L}$, late sodium current; ITP, intrathoracic pressure; LTCC, L-type calcium channel; ROS, reactive oxygen species.

afterload and transmural cardiac pressure, thereby increasing myocardial oxygen demand and precipitating subendocardial ischemia. Through mechano-electrical feedback, this increased pressure exacerbates ventricular ectopy, raises sympathetic tone, and promotes arrhythmia.[38] The summative impact of mechanical stress, ischemia, and oxidative stress causes upregulation of signaling kinases and transcription factors such as p38, c-Jun N-terminal kinases, MAPK, TNF-α, IGF-II, NF-κB, and IL-6. Maladaptive cardiac remodeling ensues with upregulation of apoptosis and subsequent myocardial hypertrophy.[39–41]

Systemic hypoxia contributes to the subendocardial ischemia that sets the stage for the structural and electrical remodeling known to predispose to SCD.[18] Additionally, intermittent hypoxia contributes to increased sympathetic tone in OSA through chemoreceptor and baroreceptor triggering, along with catecholamine release.[19] Repeat apneas and awakenings over time can alter normal hemodynamics and cause inflammatory disturbances. The resulting cardiac remodeling can be a nidus for arrhythmia, independent from that caused by OSA acutely.

There are also changes in ventricular electrophysiological properties and cardiac ion channel expression brought about by hypoxia. Intermittent hypoxia in OSA increases expression of endocardial L-type calcium channels and prolongation of the corrected QT interval (QTc) and Tpeak-Tend intervals, which are known to predispose to ventricular arrhythmias.[18,19,22] The increase in calcium channel expression is due to both hypoxia inducible factor-1 expression and direct catecholamine effects. Increasing intracellular calcium increases arrhythmogenicity via predisposing to early afterdepolarization (EAD)- and delayed afterdepolarization (DAD)-triggered activity, as well as by increasing the endocardial action potential duration (APD).[23] Increased APD itself further increases the frequency of EAD, which, in combination with a prolonged QT interval, compounds arrhythmogenicity.[19] AHI was also recently found to be inversely correlated with circulation potassium channel levels in patients with OSA, likely further contributing to prolonged cardiac repolarization.[42]

Bradycardia, atrial-ventricular block, and sinus arrest occur more often in patients with OSA,[36] with any form of heart block occurring in approximately 10% of patients with OSA.[43] Patients with OSA typically have a longer duration of heart block and at a higher frequency compared with age-matched controls.[43,44] Bradycardia creates an electrophysiologic substrate that further increases the risk

of polymorphic ventricular tachycardia; a risk further compounded by prolonged APD and increased triggered activity (**Figure 2**).

Patients with OSA have an increased incidence of, and harder-to-control, AF.[12,45] Separately, there is evidence that AF is an independent risk factor for SCD.[46–49] In a large meta-analysis of 20,918 participants, AF was independently associated with an increased risk of SCD (HR, 2.47; 95% CI: 1.95–3.13; P<0.001).[47] In the context of OSA, however, it is still unclear whether AF plays a direct role in SCD; acts as a compounding risk factor for SCD; or is simply an indicator of complex changes in the ECG substrate that occur in patients with OSA.

ECG Markers of SCD in Patients With OSA

There are multiple ECG markers of increased risk of SCD associated with OSA.[20,50] These include PVC, increased heart rate "turbulence", QT interval prolongation, AF, and T-wave alternans.[20] Atrioventricular block has also been shown to be a frequent rhythm disturbance in OSA.[43] Individuals with severe OSA have a higher risk of nocturnal cardiac arrhythmia including non-sustained ventricular tachycardia and complex ventricular ectopy.[37] Patients with these ECG abnormalities have an approximate 2-fold increase in SCD during sleep.[21]

There are robust data on increased QTc and QTc dispersion in patients with OSA.[22,46,51] Given the known association between prolonged QTc and the incidence of ventricular arrhythmia,[52–54] it is possible that SCD in OSA is in part mediated by changes in ventricular repolarization in this population. Increasing severity of OSA has been shown to be related to degree of QT interval prolongation, albeit in a cohort of patients with congenital long QT syndrome.[55] In a similar manner, the magnitude of QTc has a consistent relationship with the degree of hypoxia.[56] Given the report of patients with OSA having a predilection for SCD during sleeping hours, dynamic change in QT during these times may contribute to these events.[31,57]

The influence that OSA has on ventricular repolarization can also be seen in abnormal frontal and spatial QRS-T angle in patients with OSA. A 2018 analysis found that higher AHI was associated with greater odds of abnormal QRS-T angle.[58] It would be valuable to examine the prognostic and therapeutic implication of these ECG markers in patients with OSA. For example, patients with OSA and ventricular repolarization abnormality such as prolonged QTc or abnormal QRS-T angle may represent a higher risk subgroup for SCD.

OSA-induced hypoxia can cause ischemic changes on ECG in patients with underlying CAD.[59] These changes were reported to be relieved by continuous positive airway pressure (CPAP) in one study.[59] Changes have also been seen in acute MI, with an increase in PVC noted in OSA compared with non-OSA groups.[60] Both ischemic ventricular arrhythmias from exposure to chronic intermittent hypoxia and the nocturnal arrhythmogenic state produced by alterations of the autonomic nervous system contribute to the increase in SCD in this patient population.[19]

OSA and SCD in Patients With CHF

Sleep apnea, namely OSA, central sleep apnea (CSA), and mixed-type apnea are common in patients with CHF. Patients with both OSA and CHF are at further risk of SCD, and may represent a unique population. In patients with CHF and an implantable cardiac defibrillator (ICD), there is a higher prevalence of sleep apnea,[61,62] and the rate of appropriate defibrillation for ventricular arrhythmia (a surrogate marker for SCD) is higher in patients with sleep apnea.[48] Moreover, appropriate defibrillation in these patients has been seen to have a nocturnal predilection.[63] This emerging pattern of increased nocturnal ICD therapy and SCD coupled with a known increase in QT interval and changes in ion channel activity in OSA patients with CHF deserves further evaluation.

Impact of Sleep Apnea Treatment on SCD

Studies examining the impact of nocturnal CPAP therapy on SCD are scarce. The SAVE study, which followed patients with known CVD or cerebrovascular disease and OSA for a mean of 3.7 years, found that therapy with CPAP plus usual care did not decrease the rate of composite cardiovascular events.[64] SCD events were not assessed in that study. Intriguingly, the study remained non-significant even when only patients with >4 h of CPAP adherence were included.[64]

The recent SERVE-HF trial, which randomized patients with both CHF and CSA to treatment with adaptive servo continuous positive pressure ventilation vs. no therapy, examined appropriate ICD therapy as a component of the primary endpoint.[65] Measurement of this outcome, however, which could be viewed as a surrogate for SCD, was not completed due to early termination of the trial.[65] Interestingly, the investigators unexpectedly found that the treatment group had significantly higher rates of cardiovascular causes of death than the control group. This included death from CHF, MI, SCD, procedure-related death, stroke, and presumed cardiac cause of death.[65] Consequently, no conclusion could be derived regarding whether treatment of CSA in patients with CHF would have any impact on SCD. The ongoing ADVENT-HF trial, which includes both patients with OSA and CSA, may provide more insight into this.[66] In general, examining the therapeutic effects of intervention on SCD remains a challenge due to lack of power in typical clinical trials.

Impact of Sleep Apnea Treatment on Cardiovascular Outcomes

A 2018 meta-analysis examining the effects of CPAP on long-term cardiovascular outcomes in patients with CVD and OSA found that CPAP might prevent subsequent cardiovascular events.[67] Specifically, treatment with CPAP was associated with a significantly lower risk of major adverse cardiovascular events in six of seven observational studies (RR, 0.61; 95% CI: 0.39–0.94, P=0.02).

A similar meta-analysis by Yu et al looked at 7,266 pooled patients with sleep apnea and found that CPAP use, compared with no treatment or sham, was not associated with reduced risk of composite cardiovascular outcomes or death.[68] That meta-analysis conducted subgroup analysis for ≥4 h of adherence, and noted a significant reduction in major adverse cardiovascular events (RR, 0.58; 95% CI: 0.34–0.99). The authors of that study noted that the result may point to the importance of good CPAP adherence for achieving benefit, but also note that the result of the subgroup analysis could be related to chance. Other studies have found significantly better composite cardiovascular

outcomes when patients had ≥4 h of CPAP use per night.[69,70]

In a 2018 randomized control trial of patients with OSA, a significant reduction was noted in QTc interval by 11.3 ms with therapeutic CPAP use.[71] The change in QTc interval was most pronounced in patients with baseline QTc >430 ms and during the hours 6 p.m.–12 p.m.[71] That study provides a biological underpinning for how CPAP therapy may influence SCD. In a separate randomized study looking at CPAP therapy for OSA in CHF patients, 1 month of CPAP therapy significantly reduced nocturnal hypoxia, urinary norepinephrine, and ventricular ectopy.[72] These changes with CPAP therapy suggest a decrease in sympathetic nervous system tone. To date, no trials have been conducted that examine the impact of OSA treatment on SCD directly in the general population. The studies discussed here, however, provide an indirect look at the interactions between the entities.

Influence of Normal Sleep on Arrhythmogenicity

Even in the absence of pathologic sleep, there are sleep stage-dependent shifts in autonomic nervous system activity. Increased baroreceptor gain and vagal tone during non-rapid eye movement (non-REM) sleep increase the frequency of sinus arrhythmia and bradycardia.[73] In the context of QT interval prolongation, repolarization abnormalities, and triggered activity, hypothetically, these bradyarrhythmias can generate an electrophysiologic substrate for polymorphic ventricular tachycardia.[34,74]

With transition to REM sleep, specifically during phasic REM, sympathetic nervous system activity increases.[73,75] Although REM sleep is generally considered a sympathetic nervous system-dominant state, it also involves bursts of vagal activity, making it a period of bradyarrhythmias such as sinus pause.

Physiologic sleep affects arrhythmogenicity at the molecular level. In mice models, circadian rhythm was found to influence the expression of Krüppel-like factor 15, and, thus, kChIP2 (a voltage-gated potassium channel), which modulates ventricular repolarization normally, and can contribute to arrhythmogenicity.[76] Additional work also found that the circadian rhythm controls expression of voltage-gated sodium channels in ventricular cardiomyocytes, resulting in QRS prolongation and slowing of heart rate.[77] Changes in the complex molecular clock mediated via the circadian rhythm produce electrophysiologic changes that, in the setting of underlying cardiac disease, promote arrhythmia and may contribute to nocturnal SCD.[76,78] Therefore, the sleep state itself, independent of OSA, brings on physiologic changes that increase susceptibility to SCD.

Future Research Goals and Ongoing Studies

With the growing body of evidence elucidating the relationship between OSA and SCD, there has been a resultant rise in the number of published works involving these two conditions. There are few ongoing observational studies or clinical trials investigating their direct relationship, however, and no studies to date have been conducted using SCD as the endpoint in patients with OSA. In light of the difficulty in designing an adequately powered study evaluating the impact of OSA treatment on SCD in the general population, identification of high-risk groups would be important. Such groups may include patients with OSA who have established CAD, CHF, or baseline ECG abnormalities who could be more prone to adverse cardiovascular outcomes.

Two pertinent clinical trials are focusing on these patient populations. A European group is currently investigating patients with ischemic cardiomyopathy and OSA to further elaborate on the nature of OSA as an independent risk factor for SCD. The group is also examining if treatment of OSA with CPAP decreases the risk of SCD in ischemic cardiomyopathy patients (European Sleep Apnea and Sudden Cardiac Death Project; ESCAPE-SCD).

A separate group is targeting patients with long QT syndrome and OSA to elaborate on the extent that OSA is associated with QT prolongation, which has been posited as a key mechanism of SCD. Further, they aim to investigate the extent that treatment with CPAP changes QT prolongation (Long QT Syndrome and Sleep Apnea).[79]

More large-scale studies with long follow-up periods are needed to better understand the risk that OSA carries for SCD in specific patient populations, in addition to studies that further elaborate on the role of OSA in arrhythmogenicity.

Conclusions

The link between OSA and SCD is highly complex, and involves myocardial ischemia, maladaptive autonomic nervous system changes, altered ion channel expression, increased arrhythmogenicity, and hemodynamic shifts that act in a way that raises the biologic plausibility for a convincing link between the two conditions. There is a paucity of evidence, however, for a direct link between the two at a population level.

Recent studies underscore an interaction between sleep and SCD, but do not allow for clear conclusions on causation to be made. A growing body of evidence supports the ongoing investigation of the influence of OSA treatment on markers of SCD in both the general population and those with CVD.

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Disclosures

The authors declare no conflicts of interest.

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