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A Narrative Review of How Sleep Related Breathing Disorders and Cardiovascular Diseases are Linked: An update for advanced practice registered nurses

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Abstract

Purpose/ Objectives—Sleep-related breathing disorders (SRBDs), including obstructive sleep apnea and central sleep apnea, are common among patients with cardiovascular disease (CVD), but clinicians often do not pay enough attention to SRBDs. The purpose of this narrative review is to update advanced practice registered nurses (APRNs) on the literature focusing on the relationship between SRBDs and CVD (e.g., hypertension, heart failure, coronary artery disease, arrhythmias, and stroke) and on treatments that can improve SRBDs in patients with CVD.

Description of the project—We conducted an electronic search of the literature published between 1980 and 2016 from PubMed, Cumulative Index to Nursing and Allied Health Literature, Web of Science, Academic Search Premier, and related health resources websites to address the aims of this study.

Outcomes—Fifty-six primary research articles (42 observational studies and 14 experimental and quasi-experimental studies) were selected based on our study aims and inclusion criteria. The studies revealed that individuals with CVD are at a greater risk for SRBDs and that SRBDs can worsen CVD. The findings from the studies also suggest that positive airway treatment could improve both SRBDs and CVD.

Conclusions—This review found a close relationship between SRBDs and CVD. APRNs are in key positions to identify and help patients manage SRBDs. In particular, APRNs can educate staff and establish standards of practice to improve outcomes for CVD patients.

Keywords

apnea syndromes; cardiovascular diseases; advanced practice registered nurses

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States;¹ one in every four deaths is due to CVD. Approximately 7% of the United States population is reported to have some type of CVD including coronary heart disease, heart failure, arrhythmias, venous or artery disease, valvular heart disease, stroke, and congenital heart disease.² Clinicians are aware of the common risk factors for CVD, such as family history, high cholesterol level, high blood pressure, diabetes, and metabolic syndrome.² Sleep-related breathing disorders (SRBDs) can interfere with normal cardiovascular homeostasis and is common among individuals with CVD.³ However, many clinicians lack an accurate understanding of the relationship between SRBD and CVD.⁴

SRBD is an overarching term used to describe pauses in breathing and a decrease in the number of ventilations during sleep, which can result in negative consequences such as excessive daytime sleepiness, cognitive impairment, mood disturbance, functional decline, and worsening quality of life.⁵ It includes obstructive sleep apnea (OSA), central sleep apnea (CSA), and sleep-related hypoventilation and hypoxemic syndromes.⁶ In this paper, we focus on OSA and CSA, the most studied in SRBDs research. OSA is characterized by a crowded or completely obstructed upper airway during sleep, leading to partial (hypopnea) or complete (apnea) obstruction of airflow, lasting for ten or more seconds. The ratio of apnea and hypopnea events per hour is referred to as the apnea hypopnea index (AHI). The AHI reflects the severity of the obstruction: AHI of 5–15 (mild), 16–30 (moderate) and >30 (severe). Among research studies, individual AHI values may vary; therefore, the terms *mild*, *moderate*, and *severe* are defined by individual studies.⁷ Higher AHIs are associated with greater cardiovascular comorbidity, particularly if the AHIs are associated with significant oxygen desaturation.^{8,9} The clinical presentation of OSA includes disruptive snoring, witnessed apnea or gasping, and daytime sleepiness.¹⁰

Unlike OSA, CSA is characterized by cessation of breathing during sleep due to loss of respiratory drive.⁷ In CSA, pauses in breathing are associated with no respiratory effort. Apnea in individuals with CSA is often characterized by a crescendo-decrescendo pattern of breathing referred to as Cheyne-Stokes, with nocturnal dyspnea, witnessed apnea, fatigue, and daytime sleepiness. CSA is defined as more than five apnea events per hour of sleep, lasting 10 seconds, with the presence of frequent arousals during sleep or hypersomnolence during the day.^{7,10} CSA is less common than OSA, but it is present more often in older men with heart failure, neurologic disorders, mitral regurgitation, and atrial fibrillation.^{7,10} Individuals with CSA may also have co-existing OSA, referred to as mixed

apnea. A diagnosis of CSA requires that at least 50% of all the apneic events be central apnea.

Findings from large epidemiological studies, such as the Sleep Heart Health Study and Wisconsin Sleep Cohort Study, support clear connections between SRBDs and CVD since there is a high prevalence of SRBDs in patients with CVD. Untreated SRBDs are associated with an increased mortality risk, even after controlling for common confounders such as age, sex, and body mass index (BMI).¹¹ Untreated SRBDs increase an individual's risk for cardiovascular complications.¹⁰ Repetitive hypoxia, due to pauses in breathing and partial ventilation, affects individuals' sleep and daytime function, as well as cardiovascular homeostasis.⁷ Intermittent hypoxia can negatively affect cardiovascular endothelial function, myocardial contractility, and oxidative stress, producing systemic inflammation and reduced function of the cardiovascular system.¹²

For individuals with mild SRBDs and CVD, initial treatment consists of lifestyle modification and optimized CVD management.^{7,8} For those who have moderate to severe SRBDs, several varieties of positive airway pressure (PAP) therapy are considered: continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) and adaptive servo ventilation (ASV). Selection is based upon the specific ventilatory needs of the patient. CPAP utilizes a consistent level of air pressure to maintain an open airway during inspiration and expiration. BiPAP delivers two different (preset) levels of continuous airway pressure, keeping the airway open during inspiration and reducing the pressure during expiration. It has been effective for conditions where less pressure is needed during exhalation. ASV devices adjust air pressure to ensure consistent ventilation. Ventilation is generated when there are pauses in breathing and ventilatory pressure is reduced during a normal patient-initiated breath. ASV has been an option for treating CSA in individuals with heart failure resistant to other PAP therapies.^{12,13}

Limited awareness of the link between SRBDs and CVD may result in under recognition of SRBDs by healthcare providers among individuals with CVD. In general, SRBDs occur in approximately five percent of adults.¹⁴ Among individuals with CVD, the rate of SRBDs is considerably higher (47% to 83%).^{15–18} It is estimated that 93% of women and 82% of men with moderate to severe SRBDs have not been diagnosed, even in populations that have medical access to sleep clinics.¹⁹ Given that SRBDs are greatly under recognized, advanced practice registered nurses (APRNs) can play a key role in early diagnosis and successful management of SRBDs and improve health outcomes of individuals with CVD.²⁰ APRNs can establish systems to identify individuals who are at risk and facilitate accurate diagnosis and management. APRNs can ensure that men and women are adequately screened, and perhaps most importantly, help individuals successfully manage SRBDs. Awareness of the strong relationship between SRBDs and CVD, will help APRNs to understand the associated risks, screening recommendations, and appropriate interventions, and to apply this knowledge in their practices.

Much research has been done to describe, explain, and predict the relationships between SRBDs and CVD in medicine and epidemiology. The purpose of this narrative review²¹ is to inform APRNs of the key connections between SRBDs and CVD, and raise awareness of the

issues. We conducted a narrative literature review to provide readers with a foundation for understanding current knowledge and to identify implications for practice and research.²¹ Our specific aims are to update APRNs on literature that focuses both on 1) how SRBDs and CVD (i.e., hypertension, heart failure, coronary artery disease, arrhythmias, and stroke) are related, and 2) treatments that can improve SRBDs in patients with CVD.

Methods

Data sources and search strategy

For this narrative review, the authors searched for literature in 2015, and repeated the search in February 2016 to include the latest publications. To address aims 1 and 2, an electronic search was conducted of the literature published from 1980 to 2016 from PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Academic Search Premier, and related health resources websites. Figure 1 illustrates the flow of the literature search. We used the following search terms: sleep apnea syndromes, sleep-related breathing disorders, sleep disordered breathing, continuous positive airway pressure, CPAP, sleep apnea, heart failure, cardiovascular diseases, hypertension, high blood pressure, stroke, arrhythmias, coronary artery disease, coronary heart disease, cardiac, cardiovascular. The search yielded 2,175 articles for screening.

Articles were included if they met the following inclusion criteria: published, peer-reviewed, cross-sectional, longitudinal, experimental studies of human subjects that addressed both SRBD and CVD. We excluded qualitative studies, editorials, book chapters, dissertations, commentaries, letters to the editor, and studies focusing on infants, children, or adolescents. The most common reason for these exclusions was that the studies focused on either SRBD or CVD, not both. After a review of the 1,039 remaining abstracts, articles, and their reference lists from the search, we excluded 860 articles that were not related to our aims. After retrieving the full-length articles, we assessed 188 full-text articles to assess for quality of evidence and rated the evidence as low, moderate, high, with guidance from the Agency for Healthcare Research and Quality.²²

Results

The final selection included 56 articles, 42 observational studies and 14 experimental and quasi-experimental studies that met our inclusion criteria. Tables 1–6 include summaries of the articles synthesized for this paper. Ten articles were related to SRBDs and hypertension^{23–32}, ten articles were related to SRBDs and heart failure^{18,33–41}, nine articles were related to SRBDs and coronary artery disease^{33,36,42–48}, six articles were related to SRBDs and arrhythmia^{49–54}, seven articles were related to SRBDs and stroke^{30,55–61}, and 14 articles were related to treatment options for patients who had SRBDs and CVD.^{12,13,62–73}

Hypertension and SRBDs

The findings from large cohort studies^{23–29} and clinical studies^{30–32} have revealed strong associations between OSA and hypertension (Table 1). Researchers have investigated how OSA and hypertension are related. In cross-sectional studies using large population data, an

increase in AHI and the category of higher AHI had higher odds of hypertension than those with lower AHI, even after controlling for possible covariates.^{23,26,28} Further, individuals with OSA were found to have higher blood pressure than those without it. For instance, Hla et al.²⁴ found that the mean blood pressure was higher in the OSA group than in the control group ($p < 0.05$). Davies and colleagues³⁰ also found that the OSA group had significantly higher systolic and diastolic pressures during the day and night than the non-OSA group ($p < 0.05$).

A longitudinal study using data from the Wisconsin Sleep Cohort Study also revealed that an increase in AHI and higher AHI (e.g., 5) were associated with the development of hypertension.²⁵ Not only AHI during overall sleep stage, but also AHI during rapid eye movement sleep were found to be related to the development of hypertension ($p = 0.017$).²⁷

Heart Failure and SRBDs

There is a strong relationship between SRBDs and heart failure. Table 2 presents a summary of the articles that examined the relationship between SRBDs and heart failure. The findings revealed that the prevalence of SRBDs in heart failure patients is high, and individuals with SRBDs have a higher risk of developing heart failure than those without SRBDs.^{18,33,35,37} Up to 53% of individuals with heart failure have OSA and up to 21% have CSA, depending upon the population studied.^{18,35,37} Severe SRBDs increase the risk of developing heart failure.³⁶ Findings from a well-known longitudinal study, the Sleep Heart Health Study³³, demonstrated that individuals with severe OSA were 58% more likely to develop heart failure than those without OSA.

Not only do SRBDs and heart failure coexist frequently, but the coexistence of SRBDs and heart failure can also be detrimental to the progression of heart disease and health conditions. For instance, SRBDs are associated with negative functional outcomes in individuals with heart failure³⁸, an increase in fluid accumulations⁴¹, reductions in left ventricular ejection fraction, alterations in blood gases, increased sympathetic activity⁷⁴, impaired cognition³⁹, lower exercise capacity⁴⁰, worsen quality of life⁷⁵, and increased mortality.³⁴

Coronary Artery Disease and SRBDs

Individuals with SRBDs are at increased risk of having and developing coronary artery disease and individuals with coronary artery disease are at increased risk of having SRBDs, based on the findings of several cross-sectional^{36,42–46} and longitudinal studies^{33,47,48} using large population-based cohorts. Table 3 presents a summary of the articles related to SRBDs and coronary artery disease.

In the cross-sectional studies, up to two-thirds of individuals with coronary artery disease were found to have SRBDs, and investigators found that increases in AHI were related to increases in the risk of developing coronary artery disease (odds ratios = 3.1 and 8.7).^{42,43} Individuals with untreated severe SRBDs were 2.6 times more likely to develop coronary artery disease or have an incident of heart failure compared to those without SRBDs.⁴⁷ The findings from a longitudinal study also demonstrated that greater AHI was associated with an increased risk of developing coronary artery disease.³³

SRBDs were also related to poor health outcomes in individuals with coronary artery disease. A study using the Sleep Heart Health Study data revealed that SRBDs were associated with mortality from all causes and mortality from coronary artery disease, especially in men between ages 40 and 70 (hazard ratio = 2.09).⁴⁸ Furthermore, Saito and colleagues found that apneic episodes were related to arrhythmias among 49 individuals with previous myocardial infarctions.⁴⁵

Arrhythmias and SRBDs

The findings from the cross-sectional and longitudinal sleep studies^{49–54} demonstrated a connection between SRBDs and atrial and ventricular cardiac arrhythmias. Table 4 presents a summary of articles that explored the relationship between arrhythmia and SRBDs. In the Sleep Heart Health Study⁴⁹, individuals with SRBDs were five times more likely to have atrial fibrillation ($p = 0.003$) and ventricular arrhythmias ($p = 0.004$) than those without SRBDs. In a retrospective cohort study using longitudinal data from 3,542 adults, OSA was found to be a significant risk factor for developing atrial fibrillation (hazard ratio = 2.18).⁵⁰ The results from a large population study showed that the incident of atrial fibrillation was higher in individuals with SRBDs compared to those without (1.36 vs 0.76).⁵¹ Additionally, researchers have found that greater AHI values were associated with bradyarrhythmias.⁵³

Stroke and SRBDs

The findings from the epidemiological and clinical studies demonstrated that individuals with SRBDs have an increased risk of developing a stroke.^{30,55–61} We summarized observational studies examining stroke and SRBDs in Table 5. The studies revealed that individuals with OSA have higher risks of developing strokes.

The findings from a longitudinal study in which researchers used the Sleep Heart Healthy Study data revealed that increases in AHI were related to a higher risk of developing a stroke in men, but not in women ($p = 0.016$).⁵⁹ Yaggi et al.⁵⁵ examined longitudinal data and reported that individuals with OSA had over a two-fold risk of developing subsequent strokes than did those without OSA (hazard ratio = 2.24). Furthermore, individuals in a higher AHI quartile, had an increase in the hazard ratio of a stroke.⁵⁹ In a cross-sectional study by Davies and colleagues, individuals with OSA had a 17% higher rate of developing cerebrovascular pathology (detectable with MRI) than those without OSA.³⁰

In addition to high rates of OSA among stroke patients, the presence of OSA among stroke patients is related to poorer functional outcomes than stroke patients without OSA.⁵⁷ Furthermore, higher AHI could worsen health outcomes of stroke patients.⁶⁰

Treatment of SRBDs in the CVD

Studies show that PAP therapy can decrease the severity of SRBDs. The effectiveness of long-term PAP therapy and other treatment strategies has been tested in some patients with CVD but not all. Table 6 shows the results from the experimental and quasi-experimental studies investigating treatments for SRBDs in CVD patients. Among variety of PAP therapies, CPAP is the most studied in CVD patients. For individuals with hypertension, use of CPAP has demonstrated a modest reduction in blood pressure^{62,63}; individuals with more

severe SRBDs with resistant hypertension have demonstrated a greater reduction in blood pressure.^{64,76}

For individuals with heart failure, optimizing heart failure pharmacological treatment⁶⁶, exercise programs^{67,68}, elimination of alcohol and sedatives that cause pharyngeal collapse during sleep are effective approaches to prevent the onset of OSA.¹⁰ PAP was found to improve nocturnal oxygenation, reduce left ventricular afterload and increase the left ventricular ejection fraction.⁷⁷ Researchers have suggested that ASV is an option for treating CSA in individuals with heart failure who are resistant to other PAP therapies.^{12,13} However, Cowie et al. reported higher mortality rates in those using ASV, raising questions about the safety of this therapy.⁷⁰

For individuals with coronary artery disease and SRBDs, the research studies indicated that CPAP is the most common treatment option.^{71,72} In individuals with arrhythmia, treating SRBDs had a positive effect on arrhythmia. For instance, recurrence of atrial fibrillation one year after cardioversion was found to be significantly lower in individuals with PAP-treated OSA than in those without treatment for OSA.⁷³ PAP has been demonstrated as effective in individuals who have suffered a stroke, but the findings indicate that stroke patients have a low PAP adherence rate.⁷⁸

Discussion

In this review, we found that SRBDs are related to various types of CVD, which include hypertension, heart failure, coronary artery disease, arrhythmia, and stroke. In cross-sectional studies included in this review, the prevalence of SRBDs among individuals with CVD was high and CVD was prevalent among individuals with SRBDs. In longitudinal studies, the presence of CVD could increase the development of SRBDs, or underlying SRBDs could increase the development of CVD. These results imply that the two conditions might precipitate each other. Among the various treatment modalities, PAP therapy has been the most studied and has been shown to be effective in patients with CVD and SRBDs. Although PAP therapy needs to be further tested, using PAP therapy could not only improve SRBDs, but also improve CVD outcomes.

Our narrative review reveals that SRBDs and CVD are closely related. Both the cross-sectional and longitudinal studies indicate that the presence and severity of SRBDs are related to the risk and progression of CVD. This link could be explained by three mechanisms: 1) nighttime hypoxemia, 2) large negative changes in intra-thoracic pressure, and 3) frequent nighttime awakenings.^{5,10} First, partial or full airway obstruction during sleep reduces oxygen saturation causing intermittent hypoxemia. The hypoxemia reduces oxygen delivery to the myocardium and indirectly effects endothelial cell function, pulmonary arteriolar vasoconstriction, and sympathetic nervous system activation.

Second, during obstructive apneic events, large negative intra-thoracic pressure can be induced. During central sleep apnea, hyperpnea (an increase in the depth of respiration to meet metabolic demands) can induce large negative pressure deflation especially in the compromised lungs often found in heart failure patients. These changes in pleural pressure

are more pronounced in OSA than in CSA. An increase in intra-thoracic pressure can increase myocardial oxygen consumption and extravascular lung fluid volume, which is closely related to pulmonary edema in heart failure patients. Right ventricular filling can increase because of increased intra-thoracic pressure, resulting in a decreased left ventricular compliance and volume. Fluctuations in pleural pressure contributes to changes in right and left ventricular preload and afterload as well as increased lung pressure from increased in transmural pressure of the right and left ventricles and the pulmonary microvascular bed.

Third, individuals with SRBDs lose the essential restorative effects of sleep on the cardiovascular system due to nighttime arousals. Arousals generated from airway obstruction can contribute to significant surges in blood pressure and heart rate through the night in individuals with OSA. In CSA, individuals could wake up at the peak of hyperventilation. These awakenings from sleep are caused by increases in sympathetic activity and decreases in parasympathetic nervous system activity resulting in higher blood pressure and heart rate. The changes in sympathetic and parasympathetic nervous system activity can lead to an increase in systemic vascular resistance and left ventricular afterload, vasoconstriction with increased blood pressure, right ventricular preload, increased myocardial contractility, endothelial dysfunction, systemic inflammation, hypertrophy, tachycardia, and arrhythmias.^{5,10}

Research suggests that PAP therapy is the most effective treatment for individuals with CVD and SRBDs. Among PAP therapies, CPAP was the most studied and revealed its effectiveness in reviewed articles. However, PAP therapy is not tested in all the CVD samples and some are tested in a poor manner. More randomized controlled trials are needed to demonstrate the efficacy of PAP on each type of CVD. Proper treatment and management of SRBDs could improve symptoms of SRBDs including AHI, arousals, and oxygen saturation, and health outcomes such as exercise capacity, ejection fraction, cardiovascular symptoms, hospitalizations, and quality of life. CPAP has been effective for individuals with hypertension, heart failure, coronary artery disease, arrhythmia, and stroke. One surprising finding was the questionable effects of ASV in patients with heart failure, contradicting previous treatment recommendations.¹² ASV was found to increase mortality rates. Clinicians need to be aware of this result and be cautious when selecting ASV for heart failure patients.

Implications for practice

Individuals with CVD are at greater risk for SRBDs and those with SRBDs are at greater risk for CVD sequelae. Therefore, early identification and successful management of SRBDs is essential to maintain cardiovascular health and improve SRBDs symptoms. Early screening and diagnosis are important because too often clinicians are unaware of the prevalence of SRBDs among CVD patients. Lack of screening will delay the treatment of these co-existing conditions and increase the negative consequences. APRNs play key roles in preventing, screening, and managing individuals with SRBDs and educating patients and other health care providers.

First, APRNs can screen CVD patients by asking brief screening questions or administering standard questionnaires to evaluate risk of SRBDs during outpatient visits. During

hospitalization, APRNs can increase awareness of undiagnosed SRBDs by screening and observing for SRBDs symptoms, such as snoring, gasping, pauses in breathing, fatigue, and excessive daytime sleepiness. Second, APRNs can play a pivotal role in successful long-term management of SRBDs by working collaboratively with individuals to identify barriers and develop new management strategies to evaluate and support PAP adherence, weight management, and provider follow-ups.^{79–83}

Third, evaluating and acknowledging worsening cardiovascular symptoms (e.g., fluid accumulations, lower ejection fraction, and changes in blood gases), and cognitive and functional decline are important for individuals who have both SRBDs and CVD. SRBDs can influence both heart health and other symptoms of CVD patients, such as impaired memory and problem solving³⁹ or decreases in exercise capacity.⁴⁰ Recognition of these symptoms may improve health outcomes among CVD patients with SRBDs. Finally, APRNs can facilitate educational offerings regarding the importance of early identification and continued management of SRBDs for other healthcare team members to encourage early diagnosis and treatment.

Implications for research

To date, most of the research relative to this topic has focused on improving PAP adherence in general, and is not specific to the needs of those with CVDs. The higher rates of SRBDs in CVD, the number of associated conditions, and the unique presentation of individuals with heart failure suggest that assessment and long-term management for this population may present unique challenges that need to be investigated: CVD-specific assessment and screening methods, as well as strategies to address PAP adherence unique to individuals with CVD. In addition, more intervention studies are needed to evaluate treatment efficacy of PAP therapy in particular CVDs. Interventions led by APRNs could reduce the negative consequences from SRBDs in CVD and may reduce the rate and progression of CVD and thereby improve patients' quality of life.

Summary

We have reviewed the literature related to SRBDs in CVD and demonstrated a close link between SRBDs and CVD. APRNs can play a key role in screening, and managing individuals with SRBDs. In particular, APRNs can educate staff and establish standards of practice to improve CVD outcomes for patients. Proper screening and management of SRBDs may maintain cardiovascular health and improve symptoms, and thereby improving quality of life among individuals with CVD.

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Biographies

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Dr. Phelan is a VA geriatric sleep researcher. She is particularly interested in the relationship between sleep and cognition in older adults, including those with sleep-related breathing disorders. Dr. Phelan is affiliated with the University of Wisconsin-Madison and serves as a mentor to PhD and DNP students. She has worked as a nurse practitioner and a pain management clinical nurse specialist.

As a professor at University of Wisconsin- Madison, Dr. Lauver teaches research, theory, and health promotion across the curriculum. As a nurse practitioner in primary care, she was challenged to encourage patients' health-related behaviors. As a researcher, she has conducted theory-based studies to describe, explain, and predict peoples' health-related behaviors.

Dr. Bratzke is an assistant professor in the School of Nursing at the University of Wisconsin, Madison. Her research focuses on cognition in older adults with multimorbidity. Dr. Bratzke serves as Ms. Moon's co-advisor for her doctoral program.

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Figure 1.
Flow diagram of Literature Search

Table 1
Observational studies of sleep-related breathing disorders (SRBDs) and hypertension

Author(s) (year) and Quality of Evidence	Sample	Design	Measure of SRBDs	Outcome measures	Major Findings
Longitudinal design studies					
Peppard et al. (2000), moderate	709 adults from Wisconsin Sleep Cohort Study	Longitudinal	AHI from PSG	Treatment of hypertension by medication list and systolic and diastolic BP	Individuals with higher AHI (AHI ≥ 5) had higher rates of developing hypertension compared to those with AHI of 0 at least four years later, independent of known confounding factors.
Mokhlesi et al. (2014), moderate	1,451 adults from Wisconsin Sleep Cohort Study	Longitudinal	AHI from PSG	24-hour ambulatory BP measurements	With cross-sectional data, results demonstrated that there was a higher relative chance that hypertension was observed in individuals with AHI ≥ 15 than those with AHI <15 during rapid eye movement sleep. A twofold increase in AHI during rapid eye movement sleep was associated with 24% higher odds of hypertension. Longitudinal analysis revealed a positive association between AHI during rapid eye movement sleep and the development of hypertension.
Cross-sectional design studies					
Hla et al. (1994), moderate	147 adults from Wisconsin Sleep Cohort Study	Cross-Sectional	AHI from PSG	24-hour ambulatory BP measurements	Mean BP was significantly higher among individuals with OSA (≥ 5 apneas or hypopneas per hour of sleep) compared with those without OSA
Young et al. (1997), moderate	1,060 adults from Wisconsin Sleep Cohort Study	Cross-Sectional	AHI from PSG	BP measured during at the PSG visit	BP increased with increase of AHI. SRBDs increased the risk of developing hypertension by 3.7%.
Lavie et al. (2000), moderate	2,677 people attending sleep clinic	Cross-Sectional	AHI from PSG	BP measurement at the PSG visit and/or taking anti-hypertensive	With an increase in AHI, BP increased and number of patients with hypertension increased. AHI was related to systolic and diastolic BP, adjusting covariates.
Nieto et al. (2000), moderate	6,132 adults from Sleep Heart Health Study	Cross-Sectional	AHI from PSG	Use of hypertensive medication or the average of the second and third of 3 consecutive measurements of BP	Individuals in highest category of AHI (≥ 30 per hour) had higher odds of hypertension compared to lowest category (≤ 1.5 per hour).
Davies et al. (2001), low	45 OSA patients and 45 matched controls	Cross-Sectional	OSA diagnosed based on PSG	24-hour ambulatory BP measurement	OSA group had higher systolic and diastolic pressure during the day and night
Drager et al. (2010), moderate	99 adults from hypertension unit	Cross-Sectional	OSA diagnosed based on PSG	BP measured during PSG visit	Presence of OSA was positively associated with BP, age, obesity, dyslipidemia, resistant hypertension, and metabolic syndrome.
Cano-Pumarega et al. (2011), low	2,148 adults from Vitoria Sleep Cohort	Cross-Sectional	RDI from PSG	BP measurement during the visits	The odds ratio for hypertension incident increased with higher RDI

Author(s) (year) and Quality of Evidence	Sample	Design	Measure of SRBDs	Outcome measures	Major Findings
Walia et al.(2014), moderate	284 adults	Cross-Sectional	OSA diagnosed based on PSG	24-hour ambulatory BP monitoring and BP measurement during patient visit	Resistant, elevated BP were more prevalent in people with severe OSA than those with moderate OSA. There was a four-fold higher adjusted chance of resistant elevated BP in people with severe OSA.

AHI = Apnea Hypopnea Index; BP= blood pressure; OSA = obstructive sleep apnea; PSG = polysomnography; RDI = respiratory distress index; SRBDs = sleep-related breathing disorders

Table 2

Observational studies of sleep-related breathing disorders (SRBDs) and heart failure (HF)

Author(s) (year) and Quality of Evidence	Sample	Design	Measure of SRBDs	Outcome measures	Major Findings
Longitudinal design studies					
Javaheri et al. (2006), moderate	100 HF patients	Longitudinal	AHI from PSG	Physician diagnosed HF	A total of 49% of HF had SRBDs; 12% had OSA and 37% had CSA
Wang et al. (2007), moderate	164 HF patients	Longitudinal	AHI from PSG	Cumulative rate of death	The death rate was greater in HF patients with untreated SRBDs than those without SRBDs.
Yumino et al. (2009), moderate	218 HF patients	Longitudinal	AHI from PSG	Physician diagnosed HF	Among 218 HF patients, a total of 47 % had SRBDs; 26% had moderate to severe OSA and 21% had CSA. The prevalence of OSA and CSA did not change over time.
Gottlieb et al. (2010), moderate	4,422 adults from the Sleep Heart Health Study	Longitudinal	AHI from PSG	Records from hospital discharge records and death certificates	Men with severe OSA were 58% more likely to develop HF than those without OSA at 8.7 years of follow up
Cross-sectional design studies					
Shahar et al. (2001), moderate	6,424 adults from the Sleep Heart Health Study	Cross-sectional	AHI from PSG	Self-reported HF	Two-fold likelihood that CAD was found in individuals with AHI >11 compared to individuals with AHI 1-3, adjusting for age, race, sex, smoking, diabetes, hypertension, medications, blood pressure, body mass index, total cholesterol, and high density lipoprotein cholesterol.
Ferrier et al. (2005), low	87 HF patients	Cross-sectional	AHI from PSG	Physician diagnosed HF	Among 87 individuals 53% had OSA and 15% CSA
Redolfi et al. (2009), low	23 HF patients	Cross-sectional	AHI from PSG	Leg fluid volume from bioelectrical impedance and neck circumference	With change in AHI, there were changes in leg fluid volume and neck circumference adjusting for covariates.
Redeker et al. (2010), moderate	170 HF patients	Cross-sectional	AHI from PSG	Functional performance using six-minute walk test, daytime activity level, and medical outcomes study SF-36	HF patients with higher AHI had lower activity level. Severe AHI was associated with a four-fold likelihood of poor functional performance based on SF-36 physical function score after adjusting for related covariates. However, there was no significant relationship between AHI and 6-minute walk test.
Knecht et al. (2012), low	172 HF patients	Cross-sectional	History of sleep apnea from medical chart review	Cognitive function Neuropsychological battery	HF patients with SRBDs had lower scores on attention after adjusting for covariates than those without SRBDs.
Konecny et al. (2015), low	198 patients with cardiomyopathy	Cross-sectional	Oxygen desaturation index from overnight oximetry	Peak oxygen consumption from cardiopulmonary stress testing	Patients with SRBDs had decreased peak oxygen consumption than those without SRBDs.

AHI = Apnea Hypopnea Index; CAD = coronary artery disease; CSA = central sleep apnea; HF = heart failure; OSA = obstructive sleep apnea; PSG = polysomnography; SF-36 = short form health survey; SRBDs = sleep-related breathing disorders

Table 3
Observational studies of sleep-related breathing disorders (SRBDs) and coronary artery disease (CAD)

Author(s) (year) and Quality of Evidence	Sample	Design	Measure of SRBDs	Outcome measures	Major Findings
Longitudinal design studies					
Punjabi et al. (2009), moderate	6,441 adults from the Sleep Heart Health Study	Longitudinal	AHI from PSG	Cause of death from questionnaires or interviews. Surveillance of local hospital records and obituaries, and linkage to Social Security Administration Death master file	SRBDs were associated with all-cause mortality and specifically with mortality associated with CAD, especially in men between ages 40 and 70.
Gottlieb et al. (2010), moderate	4,422 adults from Sleep Heart Health Study	Longitudinal	AHI from PSG	First occurrence of CAD during follow up	AHI increases the risk of developing CAD in men after adjusting for age, race, body mass index, and smoking.
Cross-sectional design studies					
Saito et al. (1991), low	49 patients with acute myocardial infarction	Cross-sectional	Apneic episodes measured by using apnea monitor	Cardiac index, arrhythmias	21 out of 49 patients had capillary oxygen saturation of less than 90%. Occasionally, arrhythmias followed these episodes, such as premature supraventricular contractions, premature ventricular contraction, and ventricular tachycardia.
Moore et al. (1996), low	142 men with CAD and 50 controls without heart disease	Cross-sectional	AHI from PSG	CAD diagnosed with angiography	Men with CAD had a higher occurrence (37%) of SRBDs (AHI 10) than those in the control group (20%). Multiple regression analysis results showed that a 15-unit increase in AHI was related to an odds ratio of 2.9 for CAD.
Martinez et al. (2011), low	55 adults	Cross-sectional	AHI from PSG	Physician diagnosed CAD	An increase in AHI increases the risk of developing CAD.
Shahar et al. (2001), moderate	6,424 adults from the Sleep Heart Health Study	Cross-sectional	AHI from PSG	Self-reported CAD	Higher odds (1.27) of CAD were found in individuals with AHI >11 than those with AHI 1-3, adjusting for age, race, sex, smoking, diabetes, hypertension, medications, BP, body mass index, total cholesterol, and high density lipoprotein cholesterol.
Peker et al. (1999), low	62 adults	Cross-sectional	RDI from PSG	Physician diagnosed CAD based on standards	Approximately one-third of individuals with CAD had OSA. OSA increases the risk of developing CAD three-fold.
Glanz et al. (2013), moderate	662 adults	Cross-sectional	AHI from PSG	Physician diagnosed CAD	Approximately 64% of individuals with CAD had SRBDs.
Hla et al. (2014), moderate	1,131 adults from the Wisconsin Sleep Cohort Study	Cross-sectional	AHI from PSG	Self-reported CAD	Individuals with untreated SRBDs with AHI > 30 were more likely to have a CAD incident compared to those without SRBDs. Estimated hazard ratios of incident CAD or HF were 1.5 for AHI > 0-5, 1.9 for AHI 5-15, 1.8 for

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Author(s) (year) and Quality of Evidence	Sample	Design	Measure of SRBDs	Outcome measures	Major Findings
					AHI 15–30, and 2.6 for AHI >30 compared to individuals with AHI = 0, after adjusting for age, sex, body mass index, and smoking.

AHI = Apnea Hypopnea Index; BP= blood pressure; CAD = coronary artery disease; CSA = central sleep apnea; HF = heart failure; OSA = obstructive sleep apnea; PSG = polysomnography; RDI = respiratory distress index; SRBDs = sleep-related breathing disorders

Table 4

Observational studies of sleep-related breathing disorders (SRBDs) and arrhythmia

Author(s) (year) and Quality of Evidence	Sample	Design	Measure of SRBDs	Outcome measures	Major Findings
Roche et al. (2003), moderate	147 adults	Longitudinal	AHI from PSG	Arrhythmia by electrocardiogram	In patients with OSA, there was a higher rate of nocturnal paroxysmal asystole than those without OSA (10.6 vs 1.2%; $P < 0.02$) and the number of episodes of bradycardia and pauses increased with the severity of the OSA. With individuals with severe OSA, frequent nocturnal non-sustained supraventricular tachycardias were found.
Mehra et al. (2006), moderate	556 adults from the Sleep Heart Health Study	Longitudinal	AHI from PSG	Atrial and ventricular arrhythmias from electrocardiogram	Individuals with OSA were five times more likely to have AF than those without OSA; and individuals with OSA had a higher rate of ventricular arrhythmia than those without OSA.
Gami et al. (2007), moderate	3,542 adults	Longitudinal	AHI from PSG	AF from electrocardiogram	The probability of developing AF is greater in those with OSA than those without OSA.
Olmetti et al. (2008), moderate	257 adults with OSA	Longitudinal	AHI from PSG	Arrhythmia by electrocardiogram	46 (18.5%) of patients were found to have arrhythmia. Bradyarrhythmia was found to be higher in patients with AHI 30 than those with AHI <30. However, there was no difference in the prevalence of tachyarrhythmia by AHI.
Namvedt et al. (2011), moderate	486 adults	Longitudinal	AHI from PSG	Holter monitoring	Ventricular premature complexes (5/hour) were more prevalent in subjects with OSA compared to those without OSA (median AHI 1.4, quartiles 1 to 3 0.5 to 3.0) during the night (12.2% vs 4.7%) and day (14% vs 5.1%). In a multivariate analysis, AHI was independently associated with an increased prevalence of ventricular premature complexes at night and day controlling for covariates.
Chao et al. (2014), low	4,082 adults with SRBDs and 575,439 control group from the Taiwan National Health Insurance Research Database	Longitudinal	History of physician diagnosed SRBDs	AF from the medical chart review	Compared to those without SRBD, the occurrence rate of AF was higher in patients with SRBDs (1.3% vs. 0.7%). The AF incidences were higher in patients with SRBDs than those without (1.38 vs 0.76 per 1,000 person-years). The greater the severity of the SRBDs, the higher the risk of AF.

AF = atrial fibrillation; AHI = Apnea Hypopnea Index; OSA = obstructive sleep apnea; PSG = polysomnography; SRBDs = sleep-related breathing disorders

Table 5

Observational studies of sleep-related breathing disorders (SRBDs) and stroke

Author(s) (year) and Quality of Evidence	Sample	Design	Measure of SRBDs	Outcome measures	Major Findings
Longitudinal design studies					
Yaggi et al. (2005), moderate	1022 adults	Longitudinal	AHI from PSG	Physician diagnosed stroke and transient ischemic attack	Individuals with OSA had over a two-fold risk of developing stroke than those without OSA. Individuals with higher AHI (AHI > 36) had a greater risk of stroke or death than those with lower AHI (AHI < 3).
Hermann et al. (2007), low	31 patients with stroke	Longitudinal	Central periodic breathing and AHI from PSG	AHI measured in post stroke days Nocturnal breathing	Patients had CSA during 18% to 24% of sleep. In all patients, breathing improved during stroke recovery.
Redline et al. (2010), moderate	5422 adults from the Sleep Heart Health Study	Longitudinal	AHI from PSG	Incident of ischemic stroke	In men in the highest quartile of AHI (>19), the hazard ratio of stroke was 2.86. In men with AHI 5–25, each unit increase AHI was associated with increased stroke by 6%. In women, stroke was not associated with AHI quartiles.
Marshall et al. (2014), moderate	397 adults from the Busselton Health Study Cohort	Longitudinal	RDI from portable monitoring device	Mortality, cardiovascular and stroke events	OSA was associated with the risk of all-cause mortality, cancer incidents, and stroke, but not with cardiovascular disease events.
Cross-sectional design studies					
Good et al. (1996), low	47 patients with recent ischemic stroke	Cross-sectional	AHI from PSG	Ability to return home at discharge, continued residence at home at 3 and 12 months, functional ability at discharge, 3 and 12 months, and death from any cause at 12 months	Oximetry measures of SRBDs correlated with lower functional abilities at discharge, and 3- and 12-month follow-ups. Among patients who underwent PSG, the prevalence of severe SRBDs was 18 out of 19 patients (95%). They had an AHI of >10 events per hour of recording, 13 of 19 (68%) had an AHI >20, and 10 of 19 (53%) had an AHI >30.
Davies et al. (2001), low	90 adults	Cross-sectional	AHI from PSG	Subclinical cerebrovascular disease from magnetic resonance imaging	Patients with OSA had a 17% greater rate of subclinical cerebrovascular disease, than those without OSA.
Mansukhani et al. (2011), moderate	174 patients with stroke	Cross-sectional	OSA risk from Berlin Sleep questionnaire	Functional outcomes Acute ischemic stroke Mortality from hospital records	Among people with stroke, a previous diagnosis of OSA was related to a worse functional outcome.

AHI = Apnea Hypopnea Index; OSA = obstructive sleep apnea; PSG = polysomnography; SRBDs = sleep-related breathing disorders

Table 6
Summary of the articles for treatment studies for sleep-related breathing disorders (SRBD)

Author(s) (year) and Quality of Evidence	Sample	Design	Intervention	Measure of SRBDs	Outcome measures	Major Findings
Randomized Control Trials						
Pepperell et al. (2002), high	118 men with OSA	Randomized control trial	Nasal CPAP	AHI from PSG	24-hour ambulatory mean BP	Compared to the sub-therapeutic nasal CPAP group, the mean arterial ambulatory BP was reduced by 2.5 mm Hg. There were improvements in both systolic and diastolic BP, and during both sleep and wake in nasal the CPAP group.
Becker et al. (2003), high	60 adults with OSA	Randomized control trial	Nasal CPAP	AHI from PSG	24-hour ambulatory mean BP	AHI was reduced in both the therapeutic and sub-therapeutic groups, but more reduction on the therapeutic groups than the sub-therapeutic group (95% vs 50%). The continuous nasal CPAP group had reductions in mean arterial BP by 9.9 ± 1.4 mm Hg while there was no change in the sub-therapeutic group. There were more improvements in AHI in the nasal CPAP group than the sub-therapeutic group.
Bradley et al. (2005), high	258 HF patients	Randomized control trial	CPAP	AHI from PSG	Death or heart transplantation rates, sleep studies, ejection fraction, exercise capacity, quality of life, neurohormones	No difference in death or heart transplantation rates. Greater reduction in AHI and norepinephrine levels in the intervention group over the control group. Improvements in nocturnal oxygen saturation ejection fraction, and exercise capacity in the intervention group over the control group. There was no difference in the number of hospitalizations, quality of life, or natriuretic peptide levels between two groups.
Gary and Lee (2007), low	23 HF patients	Randomized control trial	Home based walking intervention	Only sleep patterns	Total sleep time, nocturnal awakenings, depressive symptoms, physical function, and quality of life	No differences in outcome variables. However, the intervention group had improvement in total sleep time and quality of life related to HF.
Kasai et al. (2009), high	31 HF patients	Randomized control trial	CPAP or ASV	AHI from PSG	Sleep studies, body mass index, BP, heart rate, ejection fraction, echocardiogram measures, plasma brain natriuretic peptide, exercise capacity, quality of life.	Greater reduction in AHI in the ASV group than the CPAP group. No difference in cardiac function between the two groups. Quality of life improved more in the ASV group than the CPAP group.
Lozano et al. (2010), high	96 adults with resistant hypertension and OSA	Randomized control trial	CPAP	AHI from PSG	24-hour ambulatory mean BP, daytime sleepiness	Reductions in only diastolic pressure in the CPAP group compared to the control group, but not in systolic pressure. Daytime sleepiness improved in the CPAP group.
Servantes et al. (2012), moderate	50 HF patients	Randomized control trial	Home based exercise training	AHI from PSG	Cardiopulmonary exercise testing, isokinetic strength and endurance, Minnesotans living with	Training groups showed improvement in all outcomes, including AHI, cardiopulmonary exercise testing, and quality of life.

Author(s) (year) and Quality of Evidence	Sample	Design	Intervention	Measure of SRBDs	Outcome measures	Major Findings
					heart failure questionnaire	
Cowie et al. (2015), high	1325 HF patients	Randomized control trial	ASV	AHI from PSG	Death from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, lifesaving shock), unplanned hospitalization, quality of life,	No effects on death from any cause, lifesaving cardiovascular intervention, or unplanned hospitalization between the ASV group and the control group. The risks of death from any cause or cardiovascular causes were greater in the ASV group.
Quasi-experimental design studies						
Martínez-García et al. (2007), moderate	60 adults with resistant hypertension	Non-randomized placebo control trial	CPAP	AHI from the Autoset portable plus II system	24-hour ambulatory mean BP	Reductions in nocturnal systolic pressure after 3 months of CPAP treatment
Walsh et al. (1995), low	12 HF patients	Observational study	Captopril and oxygen	AHI from PSG	Overnight oximetry, Subjective sleep measures,	With Captopril and oxygen, there were reductions in light sleep, an increase in slow wave sleep, decreases in apneic events, and reductions in total arousals.
Franklin et al. (1995), low	10 CAD patients	Pretest and posttest design	CPAP	AHI from portable monitor	Sleep studies, myocardial ischemia episodes defined by electrocardiogram	The number of myocardial ischemia episodes decreased after the treatment. Apnea and hypopnea events were reduced after the treatment.
Randerath et al. (2009), low	12 patients with mixed sleep apnea with underlying CVD	Pretest and posttest	Combination of CPAP and ASV	AHI from PSG	Sleep studies	After treatment, there was improvement in AHI, arousals, respiratory induced arousals, and oxygen saturation.
Milleron et al. (2004), moderate	54 patients with CAD and OSA	Non-randomized controlled study	Upper airway surgery or CPAP	AHI from PSG	Composite end point (i.e., Cardiovascular death, acute coronary syndrome, hospitalization due to HF, revascularization procedure)	The CPAP treatment group reduced the risk of occurrences of the composite endpoint, including cardiovascular death, acute coronary syndrome, hospitalization due to HF, and a revascularization procedure.
Kanagala et al. (2003), moderate	43 individuals with OSA and Atrial flutter	Case-control study	CPAP	AHI from PSG	Recurrence of AF Sleep study	A lower number of AF recurrences were observed in patients who were treated with CPAP compared to patients who were not treated with CPAP.

AF = atrial fibrillation; AHI = Apnea Hypopnea Index; ASV = auto-servo ventilation; BP= blood pressure; CAD = coronary artery disease ; CPAP = continuous positive airway pressure; cardiovascular disease ; HF = heart failure; OSA = obstructive sleep apnea; PSG = polysomnography; SRBDs = sleep-related breathing disorders