International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Assessment of Cardiovascular Complications in Patients with Sleep Disordered Breathing

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Abstract

This review explores the intricate link between Sleep Disordered Breathing (SDB) and cardiovascular complications. SDB, encompassing conditions like obstructive sleep apnea and central sleep apnea, is notably prevalent, especially in obese individuals. The review delves into various aspects of SDB, including its types, causes, and widespread occurrence. It highlights the significant role SDB plays in exacerbating cardiovascular issues such as hypertension, cardiac arrhythmias, and coronary artery disease. Emphasis is placed on the importance of diagnostic methods, such as polysomnography, for identifying SDB. These diagnostics are crucial for predicting and managing the cardiovascular risks associated with SDB. The research underscores the broader implications of SDB on cardiovascular health, going beyond mere sleep disturbances, and stresses the need for prompt diagnosis and treatment to mitigate these risks.

Keywords: Cardiovascular, Complications, Sleep Disordered Breathing.

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1. Introduction

Approximately 2–4% of the global population experiences Sleep Disordered Breathing (SDB), with a particular rise in prevalence among the obese. The attention towards understanding sleep apnea and hypopnea has increased due to their escalating occurrence, leading to complications that elevate mortality rates. Recurrent sleep apnea or hypopnea, even in milder forms, imposes acute stress on the cardiovascular system, contributing to conditions like hypertension, heart failure, coronary heart disease, arrhythmias, and stroke, thereby amplifying the risk of mortality [1].

2. Sleep Disordered Breathing

Sleep-disordered breathing (SDB) includes primary snoring (PS), obstructive sleep apnea (OSA), central sleep apnea (CSA), and hypoventilation disorders. Primary snoring is defined as the act of snoring without experiencing a decrease in oxygen levels or being awakened from sleep. Sleep apnea is a condition when there is a complete stop or considerable decrease in the flow of air during sleep. It is divided into three categories: obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed disease (which includes both OSA and CSA) depending on the effort required to breathe. These kinds of sleep-disordered breathing (SDB) cause physiological disruptions, such as intermittent low oxygen levels, high carbon dioxide levels, interrupted sleep, and sudden increases in stress hormones. These disturbances are thought to have a role in the development of cardiovascular disease and other related health issues. Hypoventilation syndromes, which are worsened during sleep as a result of decreased responsiveness in breathing, are included in the categories of Sleep-Disordered Breathing (SDB) [2]. The International Classification of Sleep Disorders, 3rd Edition (ICSD-3), categories Sleep-Disordered Breathing (SDB) into four subtypes: Obstructive Sleep Apnea (OSA), Central Sleep Apnea (CSA), sleep-related hypoventilation disorders, and sleep-related hypoxemia disorders (Table 1) [3].

2.1. Obstructive Sleep Apnea

Obstructive sleep-disordered breathing (SDB) is not an independent illness, but rather a syndrome that is defined by malfunction in the upper airway during sleep. This dysfunction is evident via symptoms such as snoring and greater effort in breathing, caused by heightened resistance in the upper airway and a tendency for the throat to collapse. Obstructive Sleep Apnea (OSA), commonly referred to as obstructive sleep apnea-hypopnea, is a sleep condition characterized by the interruption or substantial decrease in airflow despite continued attempt to breathe [4-5]. The term "obstructive SDB" is used to describe the presence of symptoms indicating intermittent blockage of the upper airway during sleep, without a specific severity level determined by objective tests such as polysomnography.

Obstructive Sleep Apnea is defined by the heightened susceptibility of the upper airway to collapse during sleeping, leading to significantly decreased (hypopnea) or completely absent (apnea) airflow via the nose and/or mouth. These occurrences often result in a decrease in the amount of oxygenated hemoglobin, which is generally ended by a short-lived micro-arousal. Recurrent bouts of apnea lead to prolonged reduction in oxyhemoglobin levels, disruption of sleep patterns, and decreased duration of both slow-wave and rapid eye movement (REM) sleep [6].

2.1.1. Etiology

Excessive body weight is the main contributing factor for sleep apnea, with over 58% of moderate to severe instances of obstructive sleep apnea (OSA) being linked to obesity. The cause of OSA is a mix of structural and nonstructural variables, including genetic effects [7-8]. Nonstructural risk factors for obstructive sleep apnea (OSA) include obesity, central adiposity, male gender, advanced age, postmenopausal status, alcohol use, sedative usage, and smoking. In addition, the occurrence of obstructive sleep apnea (OSA) is linked to certain medical disorders, including hypothyroidism, stroke, and acromegaly [9-10] .Although there is little data, smoking and alcohol intake are often regarded as potential risk factors for sleep apnea, especially among men. Consuming alcohol before to going to sleep worsens sleep apnea in men, whereas smoking is associated with snoring in both males and females. Research conducted on Japanese women revealed that the use of more than 23 g of alcohol per day was linked to decreased oxygen levels and the occurrence of snoring [11-12].

2.1.2. Epidemiology

Obstructive sleep apnea (OSA) is a prevalent chronic condition that impacts about one billion persons globally and imposes a substantial cost on both individuals and society. The occurrence of obstructive sleep apnea syndrome (OSAS) varied from 0.1% to 13%, with the majority of research indicating a prevalence between 1% and 4%. Benjafield et al. [13]. discovered that around 50% of males and 25% of women in the middle-aged population had been diagnosed with moderate to severe obstructive sleep apnea (OSA), as indicated by an apnea-hypopnea index (AHI) of 15 or higher. In the last three decades, there has been a significant increase in obesity rates, which has contributed to the higher occurrence of obstructive sleep apnea (OSA) [14].

2.1.3. Pathophysiology

During typical sleep, there is a reduction in muscular tension, which leads to the relaxation of the muscles in the upper airway. As a result, the air channel becomes narrower. In individuals with sleep disorders, this results in disrupted airflow, obstructive hypopneas, and apneas. Diminished neuromuscular function, particularly in those with obstructive sleep apnea (OSA), leads to the collapse of the upper airway. The Bernoulli effect, resulting from higher airway velocity, has a role in obstructive sleep apnea (OSA), especially among patients who are fat. OSA is acknowledged as a contributing factor in vascular dysfunction and hypertension [15-16].

2.1.4. Diagnosis

The symptoms of Obstructive Sleep Apnea manifest gradually and may persist for an extended period before the patient is submitted for assessment.

2.1.5. Manifestations

The nocturnal symptoms related to obstructive sleep-disordered breathing (SDB), as described by Patel and Verbraecken, include recurring loud snoring, observed episodes of apnea, disturbed sleep, increased frequency of urination throughout the night, and breathing via the mouth [17-18]. Observed episodes of apnea during sleep are regarded as the characteristic feature of obstructive sleep apnea (OSA). According to Lal et al. and Slowik et al., daytime symptoms include nonrestorative sleep (waking up as tired as when going to bed), morning headache, dry or sore throat, excessive daytime sleepiness (EDS), daytime fatigue or tiredness, cognitive deficits such as memory and intellectual impairment, and sexual dysfunction, including impotence and decreased libido [19-20]. Moreover, a past record of disruptive snoring demonstrates a sensitivity of 71% in forecasting sleep-disordered breathing (SDB). The presence of disruptive snoring together with observed apneas indicates a high specificity of 94% for sleep-disordered breathing (SDB) [17-20].

2.1.6. Physical examination

According to Slowik et al., certain physical examination findings can suggest the presence of obstructive sleep apnea (OSA) [19]. These include obesity (with a Body Mass Index exceeding 30 kg/m), a larger neck circumference (greater than 43 cm in men and 37 cm in women), and an abnormal Mallampati score that evaluates the dimensions of the upper airway. The Mallampati score classifies the visibility of the soft palate and uvula. Class 1 indicates full visibility of the soft palate, Class 2 indicates full visibility of the uvula, Class 3 indicates visibility of only the base of the uvula, and Class 4 indicates complete invisibility of the soft palate [21]. Additional physical examination findings include: swollen or "kissing" tonsils (graded as 3+ to 4+), retrognathia or micrognathia, macroglossia, a significant degree of overjet, and a high-arched hard palate. Around half of the individuals diagnosed with OSA also have systemic arterial hypertension. The Brodsky score, which is used to clinically quantify the size of the tonsils, is not a reliable indicator of the existence or severity of obstructive sleep-disordered breathing (SDB). Prior to making a diagnosis of sleep apnea, it is essential to thoroughly examine other possible contributing factors. Conditions such as bronchial asthma, gastric reflux illness, and panic disorder may cause nocturnal dyspnea. Excessive daytime sleepiness (EDS) may arise from factors such as inadequate sleep habits, substance addiction, atypical depression, and narcolepsy. Nocturia, a disorder characterized by increased urination throughout the night, is more common and tends to worsen as a person gets older. It may be attributed to several urological and medical illnesses such as benign prostate enlargement, diabetes mellitus, congestive heart failure, kidney disease, diabetes insipidus, and the use of diuretic medications [22].

2.1.7. Evaluation

The diagnosis of sleep apnea necessitates doing sleep tests, namely polysomnography, either in a laboratory setting or under ambulatory settings, in order to evaluate sleep patterns and cardiorespiratory functions. In the study of polysomnography, a respiratory event score defines an apnea as a decrease in airflow by more than 90% for a minimum duration of 10 seconds. Obstructive hypopnoeas are defined by a decrease in airflow of at least 30%, accompanied with a fall in arterial oxygen saturation of at least 3% and/or a microarousal (Figure 1) [23]. The American Academy of Sleep Medicine's guidelines, as detailed by Kapur et al., highlight the importance of polysomnography as the primary diagnostic test for adult patients who are suspected to have obstructive sleep apnea (OSA) [24]. This suggestion is derived from a thorough sleep assessment that takes into account symptoms and related co-morbidities often seen in "at-risk populations." The recommendations discourage the use of questionnaires and prediction algorithms as independent instruments for diagnosing OSA in adults. Alternatively, they propose using home sleep apnea testing with respiratory polygraphy to diagnose OSA in uncomplicated adult patients who have signs and symptoms suggesting a high likelihood of moderate-to-severe OSA. If a home sleep apnea test produces negative or unclear findings, the guidelines suggest that a follow-up polysomnography should be conducted as the next step in diagnosing obstructive sleep apnea [25].

2.2. Central Sleep Apnea

Central sleep apnea (CSA) is a condition where the respiratory rhythm generator in the pontomedullary area of the brain temporarily decreases or stops, causing interruptions in breathing during sleep. It is a kind of sleep-disordered breathing (SDB) characterized by short pauses in breathing during sleep. This sleep pattern comprises a recurring cycle of episodes with either apnea or hypopnea, followed by hyperpnea. Research findings suggest that upper airway constriction, namely at the retropalatal level, occurs during produced hypocapnic central apnea and induced central hypopnea, despite the absence of effort during central episodes [26]. Although the occurrence of CSA is less frequent compared to obstructive sleep apnea (OSA), these two diseases often occur together, resulting in individuals displaying characteristics of both illnesses. The International Classification of Sleep Disorders – Third Edition (ICSD-3) classifies CSA syndromes according to specific clinical and polysomnographic characteristics. These include Primary CSA, CSA with Cheyne-Stokes Breathing (CSB), CSA caused by a medical condition without CSB, CSA caused by periodic high-altitude breathing, CSA caused by medication or substance, and Treatment-emergent CSA [3]. The pathophysiological mechanisms behind central apneas differ depending on whether there is reduced or increased ventilation, resulting in the categorization of central sleep apnea (CSA) based on alveolar ventilation. Heart failure patients often have hypocapnia when awake, which increases their susceptibility to developing central sleep apnea (CSA) associated with hyperventilation. On the other hand, hypoventilation-related central sleep apnea (CSA) is more frequently observed in individuals with neuromuscular diseases, excessive use of medications that have side effects of depressing the central nervous system (such as opioids), cervical spinal cord injury, and structural abnormalities that affect the functioning of the lungs, such as kyphoscoliosis [27].

2.2.1. Etiology

Individuals with diverse medical disorders often experience the development of central breathing instability while sleeping, which in turn perpetuates central sleep apnea (CSA). Patients with atrial fibrillation (AF), heart failure (HF) with either preserved or decreased ejection fraction (EF), ischemic stroke, spinal cord injury, renal failure, and chronic opioid use are more likely to develop central apnea due to temporary reduction in their breathing capacity. CSA is primarily present in the majority of cardiovascular diseases and is an autonomous risk factor linked to unfavorable outcomes. Occasionally, there are cases where no clear reason can be found, and they are referred to as idiopathic or primary [28].

2.2.2. Epidemiology

The incidence of CSA often rises with advancing age and is more prevalent among those aged 65 years and older. Using a modified version of the ICSD-3 categorization, cross-sectional research found that 2.7% of males aged 65 years and older had CSA. The higher susceptibility of the aged population to acquire central apnea, especially during non-rapid eye movement (NREM) sleep, might be attributed to their comparatively heightened chemo reactivity [29]. Women have a lower susceptibility compared to males and often need a greater degree of hypocapnia in order to experience central apnea [30].

2.2.3. Diagnosis

Individuals with central sleep apnea (CSA) often report symptoms that are similar to other types of sleep apnea. These symptoms include disrupted sleep, waking up throughout the night, fragmented sleep, feeling excessively sleepy during the day, suffering morning headaches, feeling tired, and having difficulty concentrating. It is important to note that snoring is not a significant characteristic of CSA, which sets it apart from obstructive sleep apnea (OSA). Although OSA and CSA are separate conditions, they may occur together in people, resulting in a combination of features. Notably, those diagnosed with CSA had a lower prevalence of obesity in comparison to those diagnosed with OSA [26]. Underlying disease processes may cause hypercapnic central apnea, which may present with other symptoms. Patients suffering from heart failure (HF), for example, may not acknowledge or communicate their symptoms throughout the day, even when there is clear evidence of drowsiness. The absence of observed sleep disturbances in individuals with heart failure may be due to heightened daytime sympathetic activity, which boosts wakefulness and counteracts drowsiness. The level of subjective daytime drowsiness in patients with heart failure (HF) is inversely correlated with the probability of death, as stated by Kasai et al. [31].Hence, it is important to evaluate the tentative diagnosis of sleep apnea in older patients with heart failure who report feeling tired, even if they do not exhibit the usual excessive daytime sleepiness.

The identification and diagnosis of CSA in its early stages might be difficult when relying exclusively on symptoms described by the individual. This highlights the significance of nocturnal polysomnography (PSG) as the

most reliable diagnostic technique for assessing central apnea, according to Baillieul et al. [32].

3. Objective Assessment Methods for Sleep-Disordered Breathing

Three frequently used screening instruments for sleep-disordered breathing (SDB) include the STOP-BANG questionnaire, the Berlin questionnaire, and the Epworth Sleepiness Scale (ESS). The widely used STOP-BANG questionnaire has eight questions that assess snoring, daily weariness, observed apneas, therapy for high blood pressure, BMI, age, neck size, and gender. If there are three or more items present, it indicates the need for polysomnography (PSG). The STOP-BANG method demonstrates a direct relationship between sensitivity and the severity of obstructive sleep apnea (OSA). Nevertheless, the diagnostic use of this tool is restricted due to its limited specificity [33-35]. The Berlin questionnaire is a subjective evaluation consisting of 11 questions that aim to categorize the likelihood of obstructive sleep apnea (OSA). The screening process includes assessing characteristics such as snoring, observed episodes of interrupted breathing during sleep, excessive daytime tiredness, drowsiness, elevated blood pressure, and body mass index [36-37]. The Epworth drowsiness Scale (ESS) is a survey that evaluates the level of drowsiness throughout the day under different circumstances. An analysis of 212 patients revealed that the STOP-BANG questionnaire had superior specificity compared to both the ESS and the Berlin questionnaire. Nevertheless, the ESS is constrained by its antiquity and inquiries that may not accurately capture contemporary society. The interpretation of results may be affected by significant use of coffee, and some patients with a normal Epworth Sleepiness Scale (ESS) score have reported experiencing symptom relief after treatment [38-42].

4. Sleep testing and evaluation

Scalzitti et al., emphasized that there are two main methods of sleep testing: polysomnography (PSG) and home sleep apnea testing (HSAT) [43]. Polysomnography (PSG), which is conducted in a laboratory setting, is considered to be more precise. However, for people without medical issues, Home Sleep Apnea Testing (HSAT) is the recommended option because to its cheaper cost and simpler administration. It is important to understand that HSAT does not directly assess sleep using EEG, which may result in a lower evaluation of the severity of the condition compared to PSG, particularly when there is also insomnia present. If there is a strong likelihood of sleep-disordered breathing (SDB) after a negative or inconclusive home sleep apnea test (HSAT), it is advisable to have a polysomnography (PSG) as indicated by Light et al. [44]. For persons who have notable cardiac illness, neurological or neuromuscular problems, or suspected hypoventilation syndrome, it is recommended to have polysomnography (PSG), ideally with capnometry if it is accessible. In addition, PSG is advised for children and adolescents who are suspected of having sleep-disordered breathing (SDB), since the results from home sleep apnea tests (HSAT) are still developing for these age groups. There are many kinds of Home Sleep Apnea Tests (HSAT), including conventional versions that measure airflow, chest wall expansion, and pulse oximetry. WATCH-PAT and similar models estimate the apnea-hypopnea index (AHI) by assessing indicators of sympathetic activity [45]. The relationship between sleep disordered breathing and cardiovascular diseases Sleep-disordered breathing (SDB) causes sleep deprivation, intermittent hypoxia, and fluctuations in negative pressure within the chest. These factors can potentially result in detrimental cardiovascular conditions, such as sudden death, atrial fibrillation, stroke, and coronary artery disease, ultimately leading to heart failure. The study conducted by Cowie et al. [46] has shown that continuous positive airway pressure (CPAP) treatment for sleep-disordered breathing (SDB) has beneficial benefits, including the reduction of systemic blood pressure and improvement of endothelial function. Endothelial dysfunction, which is caused by oxidative stress, systemic inflammation, and sympathetic nervous system activation, is affected by variables associated to sleep-disordered breathing (SDB) such as intermittent hypoxia, sleep loss, and arousals. The occasional hypoxia seen in obstructive sleep apnea (OSA) might activate inflammatory pathways that could contribute to the development and progression of atherosclerosis. The degree of SDB is linked to endothelial dysfunction, as assessed by flow-mediated dilatation, and arterial stiffness, as assessed by the cardio-ankle vascular index. Sleep-disordered breathing (SDB) leads to oxidative stress and systemic inflammation, which in turn causes an increase in the thickness of the intima-media layer of cerebral arteries. Markers indicating oxidative stress and inflammation are shown to be associated with hypoxia caused by sleep-disordered breathing and the thickness of the intima-media layer of blood vessels [47]. Patients diagnosed with obstructive sleep apnea (OSA), even in the absence of other recognized risk factors for arteriosclerosis, have elevated intima-media thickness. This thickness is directly associated with the degree of nocturnal hypoxia. In males under the age of 65, a twofold increase in the Apnea-Hypopnea Index (AHI) is linked to a 19% rise in coronary artery calcium. Similarly, in women of all ages, a doubling of the AHI is connected with a 17% increase in coronary artery calcium. The degree of subendocardial viability defect (SDB) is strongly associated with the severity of coronary atherosclerotic load, as shown by the Gensini score. In addition, individuals with stable coronary artery disease (CAD) and different levels of sleep-disordered breathing (SDB) severity have been shown to have higher levels of troponin T, which is a marker of silent myocardial ischemia and small-scale myocardial damage [48-49]. PAI-1, plasminogen activator inhibitor-1; ROS, reactive oxygen species; NO, nitric oxide; FMD, flow-mediated dilatation; IMT, intima-media thickness; PWV, pulse wave velocity; CAVI, cardio-ankle vascular index.

5. Mortality

The Multi-Ethnic Study of Atherosclerosis (MESA) included more than 5,000 individuals who did not have any known cardiovascular disease (CVD) at the beginning of the study.

The study found that if a physician diagnosed a participant with obstructive sleep apnea (OSA), it increased their risk of death by 2.4 times and also increased their chances of developing CVD over a period of 7.5 years. The correlation was stronger among persons with an Apnea-Hypopnea Index (AHI) greater than 30, whereas lower or

inconsistent correlations were seen for less severe types of Obstructive Sleep Apnea (OSA) [51]. Untreated severe obstructive sleep apnea (OSA) in males was associated with a 2.9-fold higher risk of fatal cardiovascular disease (CVD) events compared to untreated individuals with mild or moderate OSA. Untreated severe obstructive sleep apnea (OSA) in women was linked to a death rate that was 3.5 times greater compared to female control patients, according to a study by Campos-Rodriguez et al. [52]. Studies conducted by Cowie et al., have shown that individuals with severe obstructive sleep apnea (OSA) have a three times greater risk of dying from any cause compared to those without OSA. Furthermore, the risk of dying from cardiovascular disease (CVD) is somewhat higher in those with severe OSA [46].

6. Hypertension

Approximately half of people diagnosed with obstructive sleep apnea (OSA) also have hypertension, whereas around 30% of those diagnosed with hypertension are likely to have OSA. Patients with untreated obstructive sleep apnea (OSA) who are observed over a period of 4 years are at a 2- to 3-fold higher risk of acquiring new-onset hypertension. Obstructive sleep apnea (OSA) has been identified as a major contributing factor to resistant hypertension, especially in individuals of African descent. This population is known for having a high prevalence of undiagnosed OSA, poorly managed hypertension, and complications related to high blood pressure, as highlighted by Johnson et al. [53]. A recent comprehensive analysis of many studies found a significant connection between essential hypertension and different levels of obstructive sleep apnea (OSA) severity, ranging from mild to severe OSA [54]. Nevertheless, the results of a randomized controlled trial (RCT) investigating the occurrence of hypertension and cardiovascular disease (CVD) events in patients with obstructive sleep apnea (OSA) who do not experience excessive daytime sleepiness, demonstrated that the use of continuous positive airway pressure (CPAP) did not result in a significant decrease in either of these outcomes during a median follow-up period of 4 years, as reported by Barbé et al. [55].

7. Cardiac arrhythmia

The intricate and ever-changing foundation for arrhythmias caused by OSA, which is marked by both structural re-modelling and temporary electrical alterations associated with apnea, is summarized in Figure 3 [56].

8. Atrial fibrillation

Patients with obstructive sleep apnea (OSA) have significant alterations in the structure of the atria and anomalies in the conduction of electrical signals, but there are no changes in the time it takes for the atria to recover after each heartbeat. OSA may also enhance the production of AF triggers in the pulmonary veins and other locations. Furthermore, episodes of obstructive respiratory events may cause temporary alterations in the electrical activity of the heart that can lead to arrhythmias. This may help explain why there is a higher risk of nocturnal paroxysms of atrial fibrillation that are connected to these events [57]. In the VARIOSA-AF research (Figure 4), it was shown that nights with more severe sleep apnea were associated with a 2.3-fold higher chance of experiencing atrial fibrillation (AF) for at least one hour on the same day, compared to nights with the highest sleep quality (Figure 5) [58-59]. The occurrence of sleep-disordered breathing (SDB) in individuals with atrial fibrillation (AF) varies between 21% and 74%, which is higher than the occurrence in those without AF (ranging from 3% to 49%). In addition, those with severe obstructive sleep apnea (OSA) have a reduced response to antiarrhythmic medication treatment, and those with OSA had a 31% greater risk of AF-recurrence following pulmonary vein isolation compared to individuals without OSA. Research has shown that the use of continuous positive airway pressure (CPAP) is linked to a decrease in the frequency of atrial fibrillation (AF) episodes after cardioversion, as well as a decreased risk of AF recurrence after pulmonary vein isolation. Non-CPAP therapies, such as weight reduction achieved by behavioral modifications or bariatric surgery, together with abstaining from alcohol, have shown beneficial outcomes for obstructive sleep apnea (OSA) and contribute to the preservation of normal heart rhythm. Linz, Baumert, et al. and Moula et al., propose that atrial fibrillation (AF) may increase the likelihood of developing central sleep apnea (CSB) by using processes like to those seen in heart failure [60-61]. In heart failure, elevated pulmonary vascular pressure induces excessive breathing and reduced carbon dioxide levels (hypocapnia). Alternatively, CSB may enhance the likelihood of AF by causing hypocapnia and heightened electrical instability. Autonomic dysfunction is suggested as a shared predisposing factor for both CSB and AF, as shown in idiopathic CSB.

9. Ventricular arrhythmia

In patients suffering from obstructive sleep apnea (OSA), the fluctuations in intrathoracic pressure that occur during obstructive apneas lead to changes in ventricular repolarization, which may raise the likelihood of sudden cardiac death. An analysis of more than 10,000 individuals who underwent polysomnography revealed that an apnea-hypopnea index (AHI) of 20/h is a separate risk factor for sudden cardiac death. The simultaneous presence of heart failure (HF) and sleep apnea significantly increases the likelihood of developing life-threatening ventricular arrhythmia [62]. Severe obstructive sleep apnea (OSA) is linked to an increased likelihood of experiencing ventricular premature beats, non-sustained ventricular tachycardia, and sudden cardiac death during sleep. Registry data suggests that the use of servo-assisted breathing in patients with heart failure and implanted cardioverter-defibrillator devices may decrease the need for implantable cardioverter-defibrillator therapy in the treatment of central sleep apnea (CSB). Nevertheless, it is important to mention that a comprehensive randomized study of this treatment documented a rise in cardiovascular disease (CVD) and death from all causes [63-64].

10. Coronary-artery disease

Research including more than 1,400 individuals has shown that obstructive sleep apnea (OSA) is related with a significantly increased risk of coronary events. After accounting for conventional risk variables, OSA was shown to be connected to a twofold increase in cardiovascular disease (CVD) events or death. Approximately 40% of persons with ST-segment elevation myocardial infarction (MI) had undetected severe obstructive sleep apnea (OSA).

Patients who have obstructive sleep apnea (OSA) who are hospitalized for myocardial infarction (MI) without a previous diagnosis are at a higher risk of experiencing a heart attack during the night. This may be attributed to the acute stress caused by obstructive apneas, which lead to reduced oxygen levels, increased adrenaline release, and changes in blood flow dynamics [63,65]. During a four-year study of individuals who had experienced a myocardial infarction (MI), it was found that the degree of nocturnal hypoxemia and excessive daytime sleepiness (EDS) were identified as separate factors that might predict major adverse cardiovascular events (MACE). Subjects suffering from obstructive sleep apnea (OSA) had indications of heightened arterial stiffness, premature atherosclerosis, calcification of the coronary arteries, instability of coronary plaques, and increased susceptibility of plaques. Individuals with moderate-to-severe obstructive sleep apnea (OSA) had a significantly higher degree of coronary artery disease severity, irrespective of other risk factors. Acute increases in blood pressure, low levels of oxygen in the blood, and activation of the adrenergic system during periods of breath-holding may potentially initiate cardiac ischemia or the rupture of arterial plaques. The study conducted by Ishiwata et al., found that the severity of nocturnal oxygen desaturation, rather than the apnea-hypopnea index (AHI), was a strong predictor of the development of nocturnal ST-segment depression in patients with obstructive sleep apnea (OSA) [66]. OSA is associated with higher mortality rates after a myocardial infarction (MI) and an increased risk of cardiovascular disease (CVD) following coronary intervention. During research that included more than 1,300 patients who had polysomnography, it was shown that over 45% of them had an Apnea-Hypopnea Index (AHI) of 15 or higher per hour. Additionally, it was observed that Obstructive Sleep Apnea (OSA) was independently linked to an increased risk of Major Adverse Cardiovascular Events (MACE). A second meta-analysis, which specifically examined the impact of obstructive sleep apnea (OSA) after percutaneous coronary intervention, found that it was associated with a higher risk of major adverse cardiovascular events (MACE). However, there was no significant increase in the risk of readmission due to heart failure or stroke [67].

11. Heart failure

Sleep-disordered breathing (SDB) is common in heart failure (HF), impacting 50%-75% of patients with decreased ejection fraction (HFrEF) and HF with intact ejection fraction. The prevalence of acute decompensated heart failure varies from 44% to 97%. There is a strong connection between sleep-disordered breathing (SDB), which includes both obstructive sleep apnea (OSA) and central sleep apnea (CSA), and certain variables such as obesity, being male, having atrial fibrillation (AF), being older, and having impaired left ventricular (LV) systolic performance among patients with heart failure with reduced ejection fraction (HFrEF). Significantly, the occurrence of CSA tends to increase as the clinical severity of HF rises, reflecting the underlying heart dysfunction. Significantly, SDB is autonomously associated with an increased risk of death [68-70].

12. Pulmonary arterial hypertension

Intermittent hypoxia during obstructive sleep apnea (OSA) episodes may lead to transient increases in pulmonary artery pressures due to hypoxic vasoconstriction. The persistence of these transient elevations and their contribution to sustained vasoconstriction remain unclear. While OSA frequently coexists with pulmonary or systemic hypertension, the exact role of OSA in driving this association remains uncertain. Nonetheless, it is crucial to identify pulmonary hypertension in OSA patients, as they face an elevated risk of mortality. Reports suggest a prevalence of around 20% for pulmonary hypertension (defined as pulmonary artery pressures ≥20 mm Hg) in patients with OSA, irrespective of coexisting lung disease [71-72].

13. Prognostic markers

Numerous studies emphasize that markers of overnight hypoxemia offer better prognostic value than the Apnea-Hypopnea Index (AHI), underscoring the pivotal role of cyclical oxygen saturation changes in inflammation, oxidative stress, and sympathetic nervous system activation. Polysomnographic parameters, including the Oxygen Desaturation Index (ODI), total sleep time, diastolic blood pressure dipping, time with oxygen saturation below 90% (T<90%), arousal index, and pulse rate variability, are crucial for assessing cardiovascular complications in sleep-disordered breathing (SDB) patients [73-75]. ODI quantifies the frequency and severity of oxygen desaturation events during sleep, indicating an increased risk of cardiovascular complications with higher values ([76-77]. Total sleep time, reflecting the duration of sleep during polysomnography, correlates with cardiovascular health, emphasizing the negative impact of sleep deprivation on sympathetic activity and inflammation [78-79]. Diastolic blood pressure dipping measures the physiological nocturnal decrease in blood pressure, with impaired dipping associated with elevated risks of cardiovascular diseases [80-81]. T<90% signifies the duration of oxygen saturation below 90%, indicating the severity of hypoxemia and its potential cardiovascular impact [82]. The arousal index measures sleep disruptions, influencing cardiovascular complications due to sleep fragmentation, increased sympathetic activity, and inflammation [82-83]. Pulse rate variability (PRV), reflecting the balance between sympathetic and parasympathetic activity, is elevated in SDB patients and correlates with cardiovascular morbidity and mortality [84-87]. Large-scale studies have highlighted the superiority of these parameters over AHI in predicting mortality, underscoring the importance of their comprehensive assessment for cardiovascular risk stratification in SDB patients [74,88-92].

Table 1: Classifications of sleep-disordered breathing according to the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) [3].

Primary snoring	
Obstructive sleep apnea	Obstructive sleep apnea

	Adult Pediatric
Central sleep apnea	Cheyne-Stokes breathing Apnea caused by medical conditions Medication-induced or substance-induced apnea Periodic breathing in high altitudes Primary central apnea refers to a condition characterized by the absence of breathing efforts during sleep, which is not caused by any underlying medical condition. Infantile central apnea Premature apnea Central apnea that arises as a result of treatment
Hypoventilation	Obesity hypoventilation syndrome Congenital central alveolar hypoventilation syndrome Delayed development of central hypoventilation with malfunctioning of the hypothalamus Idiopathic central alveolar hypoventilation refers to a condition when there is unexplained reduced breathing in the small air sacs of the lungs. Medication or substance-induced hypoventilation Medical conditions causing hypoventilation
Others	Sleep-related hypoxemia disorder

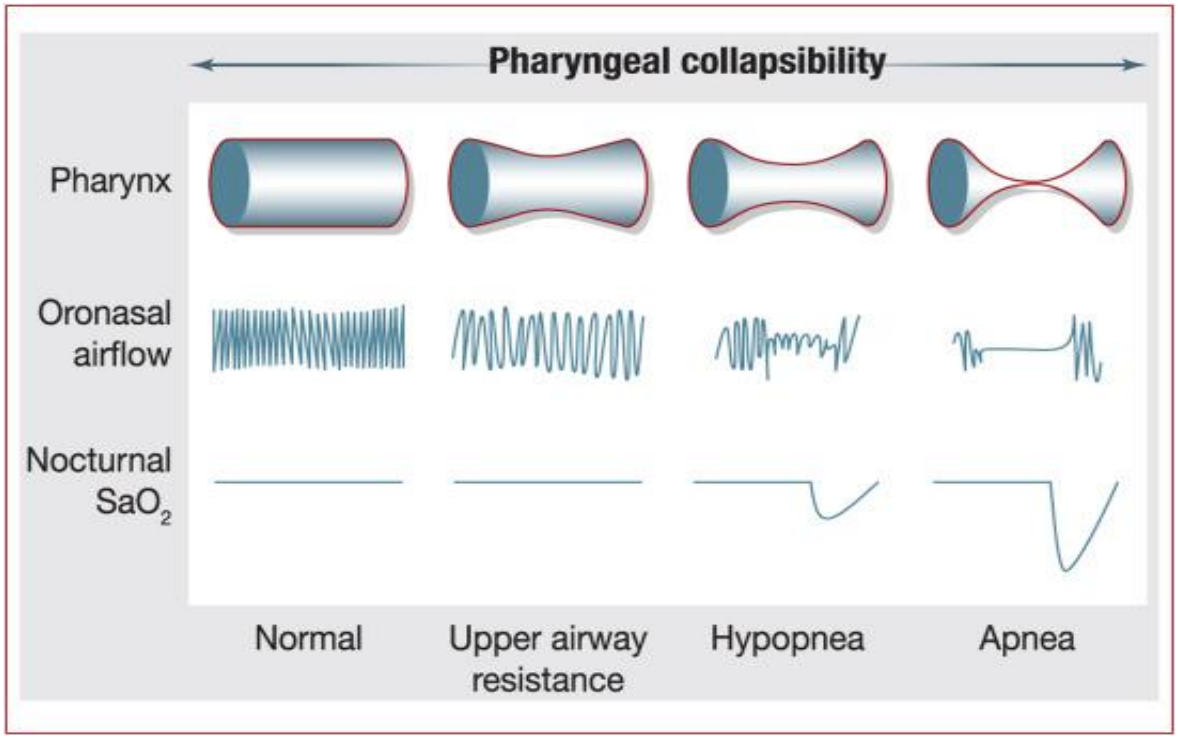

Figure 1: The severity of respiratory episodes in obstructive sleep apnea is determined by the degree of pharyngeal collapse. The presence of obstructions in the pharynx is directly connected to disruptions in the passage of air via the mouth and nose. In situations of severe pharyngeal collapsus, the passage of air via the mouth and nose is completely blocked. The level of blockage and restriction in airflow via the mouth and nose are directly linked to a greater decline in oxygen levels throughout the night (SaO2) [24].

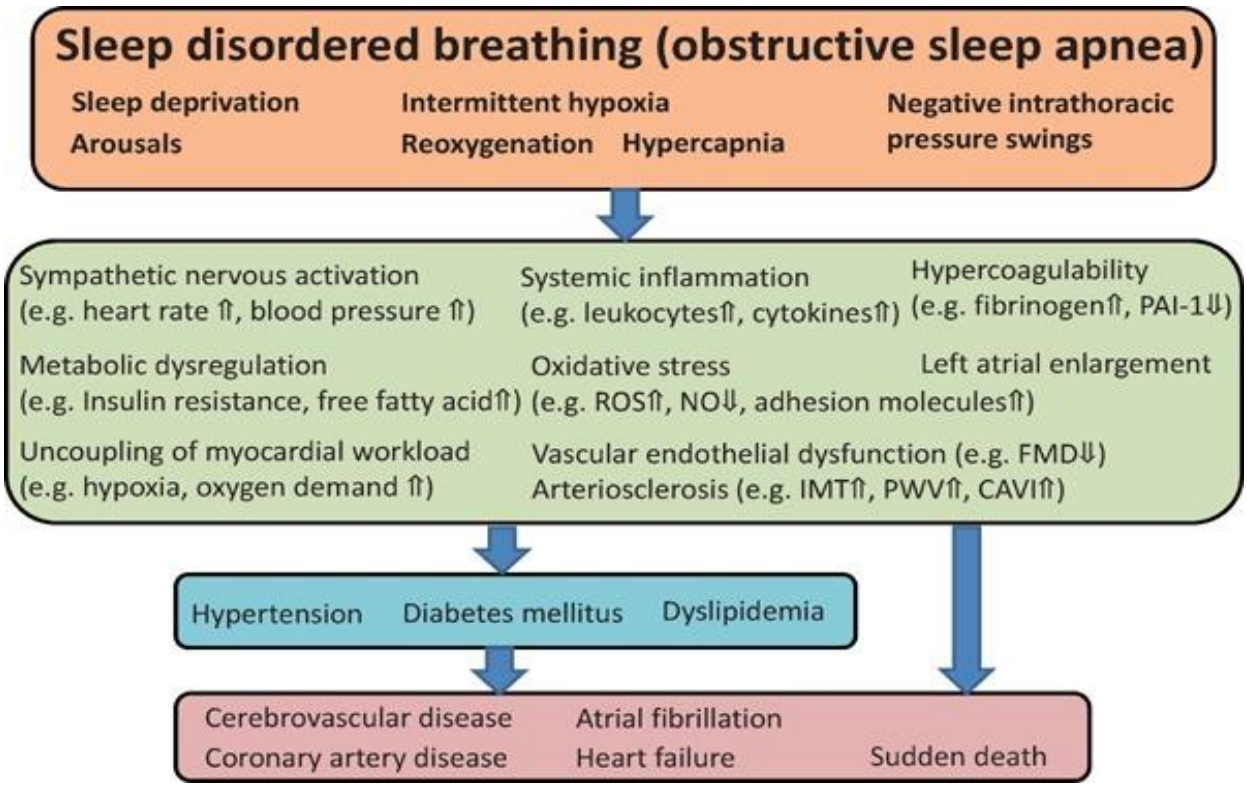

Figure 2: Pathophysiology of the impact of sleep disordered breathing, OSA, on cardiovascular disease [50].

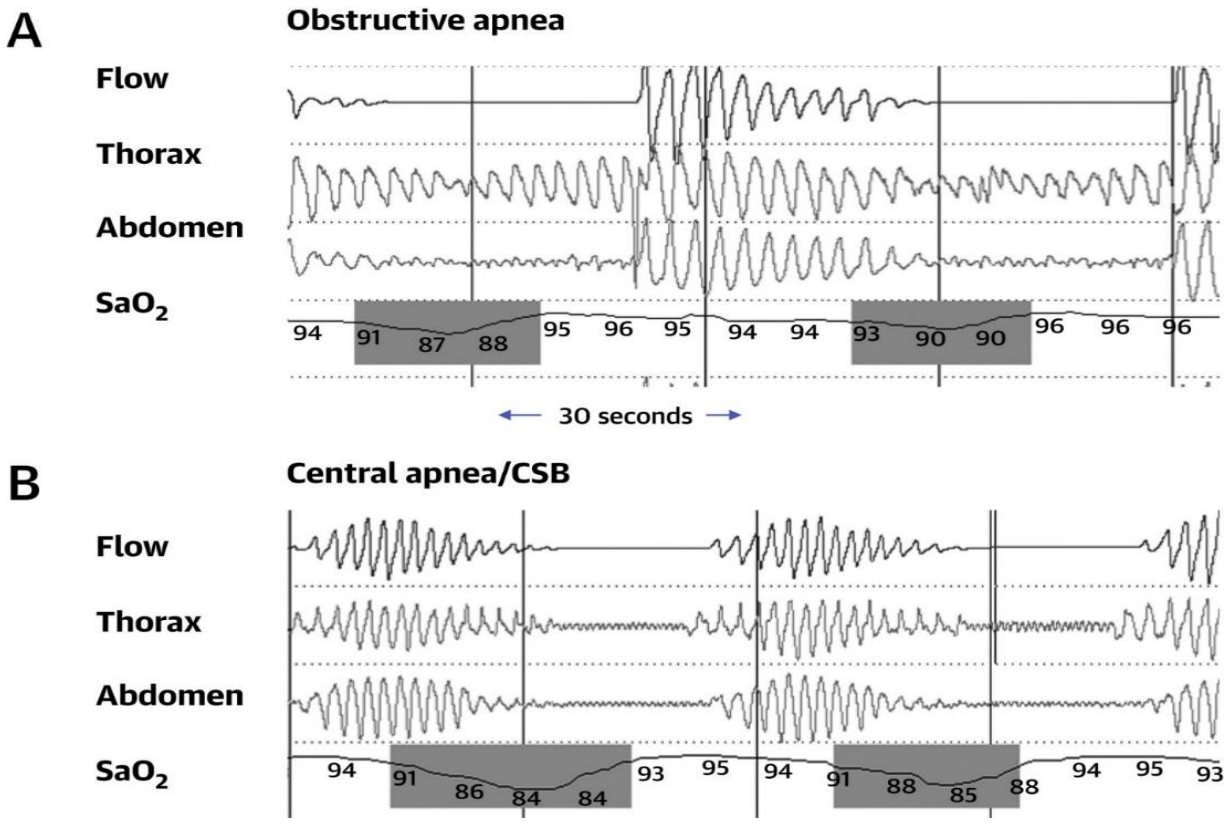

Figure 3: Features of Home Sleep Apnea Testing Traces (A) Patient diagnosed with Obstructive Sleep Apnea (OSA); (B) a patient diagnosed with Central Sleep Apnea (CSA), displaying airflow, thoracic and abdominal wall movements, and Pa02 (arterial oxygen partial pressure). It should be noted that desaturation is postponed in central sleep apnea (CSA) because to the prolonged circulation time associated with heart failure [46].

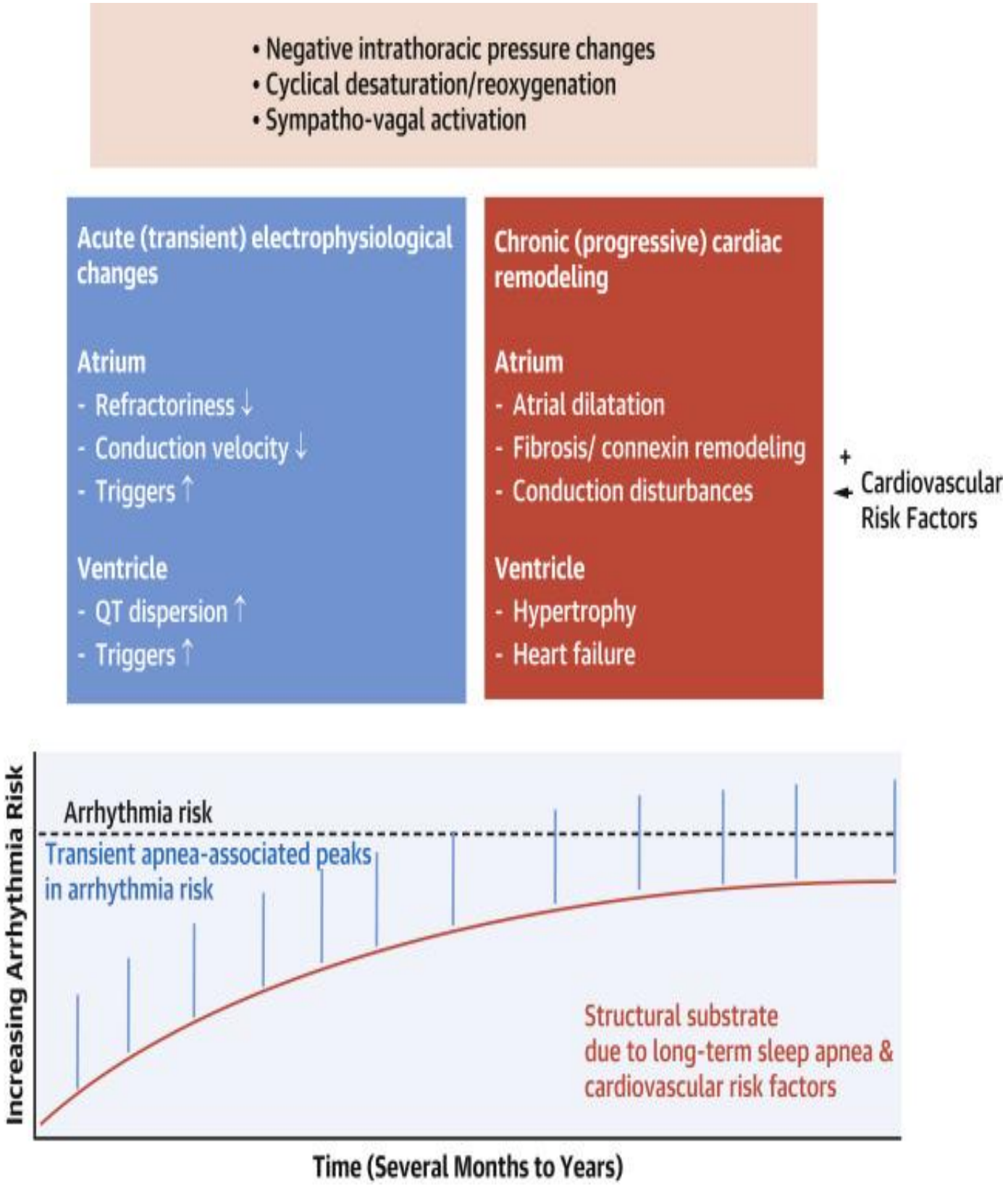

Figure 4: The intricate and ever-changing foundation for arrhythmia caused by sleep apnea. (Top) Sleep apnea leads to acute and temporary abnormalities in the electrical activity of the body (blue box) and long-term changes in the structure and function of the heart (red box). (Bottom) Each instance of acute sleep apnea leads to temporary increases in the risk of arrhythmia (shown by blue lines). However, if there is no underlying structural issue, the essential threshold to start an arrhythmia (represented by the dashed black line) cannot be achieved. Nevertheless, when there is structural re-modelling caused by chronic sleep apnea and cardiovascular risk factors (shown by the red line), sudden bouts of sleep apnea might provoke arrhythmia [46].

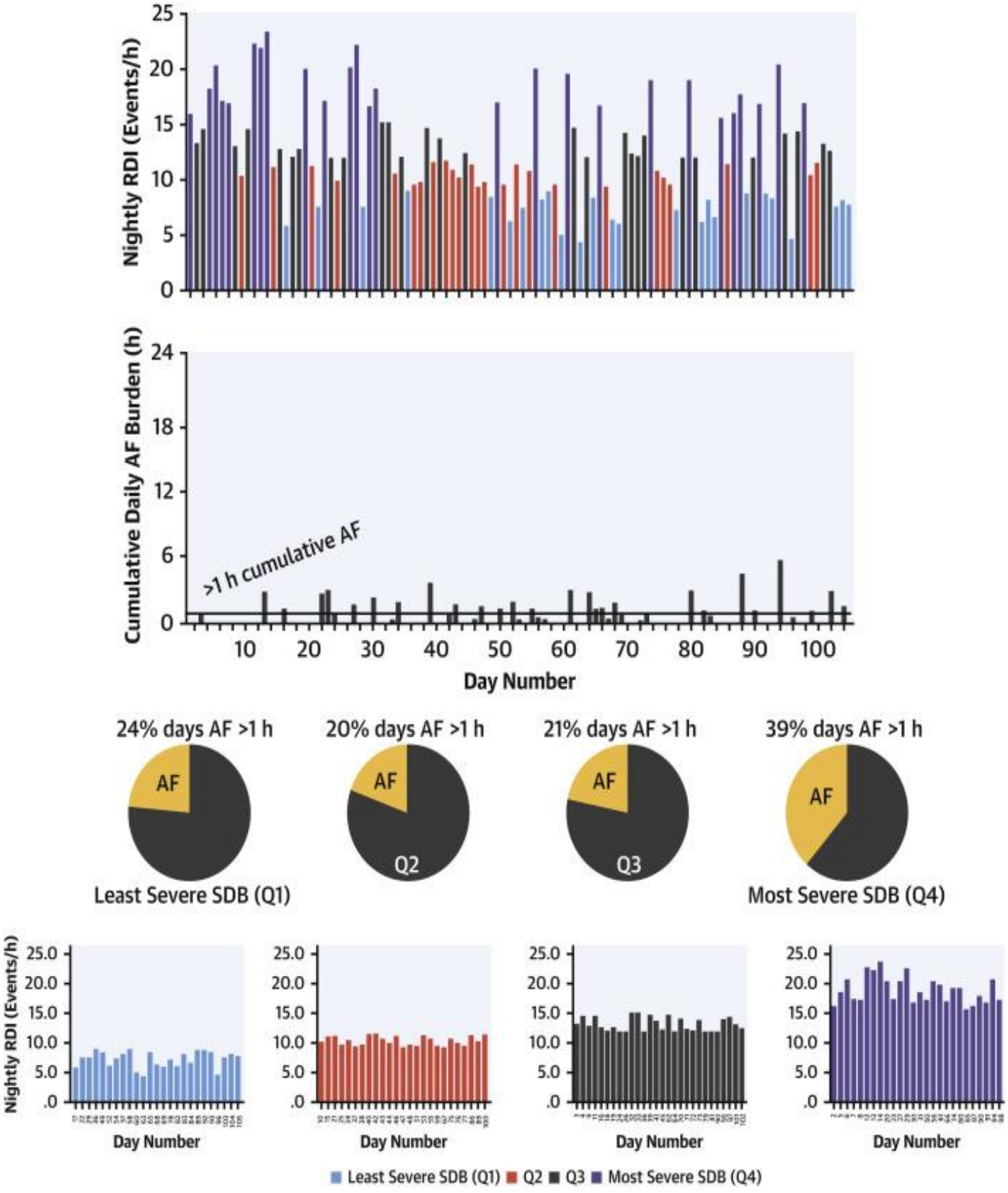

Figure 5: Concurrent, persistent daily fluctuations in both sleep apnea and episodes of atrial fibrillation. Patients who had pacemakers implanted had significant nightly fluctuations in the severity of sleep apnea. A greater respiratory disturbance index (RDI) was shown to be linked to an increased likelihood of experiencing atrial fibrillation (AF) on the same day [59].

4. Conclusions

This comprehensive review underscores the significant interplay between Sleep Disordered Breathing (SDB) and various cardiovascular complications. It illuminates the critical role of SDB, particularly in conditions like obstructive and central sleep apnea, in exacerbating cardiovascular risks such as hypertension, cardiac arrhythmias, and coronary artery disease. The findings highlight the necessity for early and accurate diagnosis of SDB through methods like polysomnography, emphasizing their crucial role in predicting and managing associated cardiovascular risks. Importantly, the review calls for heightened awareness and proactive management strategies in clinical practice to mitigate the cardiovascular impact of SDB. It also suggests avenues for future research, particularly in developing more effective diagnostic tools and treatment modalities to address the intertwined challenges of SDB and cardiovascular diseases.

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