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# A Correlation Between the Severity of Sleep-Disordered Breathing and the Frequency and Duration of Bradyarrhythmias in Patients with Cardiovascular Risk Factors: A Systematic Review

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## ABSTRACT

**INTRODUCTION :** Sleep-disordered breathing (SDB) is a highly prevalent condition strongly associated with cardiovascular morbidity. While its link to tachyarrhythmias is well-established, the relationship with bradyarrhythmias is less synthesized. This systematic review aims to evaluate the correlation between SDB severity and the frequency and duration of bradyarrhythmias in patients with cardiovascular risk factors.

**METHODS :** A systematic search of PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library was conducted for observational studies and clinical trials investigating the association between SDB severity and bradyarrhythmic events in adults with cardiovascular risk factors. Study selection, data extraction, and risk of bias assessment using the ROBINS-I tool were performed independently by two reviewers, adhering to PRISMA 2020 guidelines. Outcomes of interest included the incidence, frequency, and duration of sinus bradycardia, sinus pauses/arrest, and atrioventricular (AV) block,

as well as mean/minimum nocturnal heart rate and adjusted risk estimates.

**RESULTS :** The evidence consistently demonstrates a high comorbid disease burden, with a pooled prevalence of nocturnal bradycardia in patients with obstructive sleep apnea (OSA) of approximately 69.8% and a pooled prevalence of OSA in patients with bradycardia of 56.8%. A significant dose-response relationship was identified, with increasing SDB severity, measured by the Apnea-Hypopnea Index (AHI) or Oxygen Desaturation Index (ODI), correlating with a higher frequency and duration of bradyarrhythmic events. Patients with severe SDB had significantly higher odds of experiencing sinus pauses greater than 3 seconds (OR, 10.26; 95% CI, 2.18–48.40) and sinus bradycardia below 40 bpm (OR, 3.00; 95% CI, 1.36–6.60) compared to those with no or mild SDB. The highest prevalence and severity of SDB were observed in patients paced for high-degree AV block.

**DISCUSSION :** The synthesized evidence supports a strong, dose-dependent relationship between SDB severity and the burden of nocturnal bradyarrhythmias. This association is primarily driven by intermittent hypoxia-induced vagal hyperactivity. The high prevalence of undiagnosed SDB in patients receiving pacemakers suggests that SDB may be a significant, reversible cause of bradyarrhythmias, potentially leading to avoidable implantations. Discrepancies between community-based and clinic-based cohort studies suggest that the arrhythmogenic risk of SDB is magnified in patients with a higher burden of underlying cardiovascular disease.

**CONCLUSION :** The severity of SDB is a significant predictor

of the frequency and duration of nocturnal bradyarrhythmias in patients with cardiovascular risk factors. Systematic screening for SDB is warranted in patients presenting with significant nocturnal bradycardia or AV block to identify a modifiable cause and potentially alter therapeutic management, including the need for permanent pacing.

**KEYWORDS :** Sleep-Disordered Breathing, Obstructive Sleep Apnea, Bradyarrhythmia, Sinus Arrest, Atrioventricular Block, Cardiovascular Risk, Systematic Review

# INTRODUCTION

## The Intersecting Epidemics of Sleep-Disordered Breathing and Cardiovascular Disease

Sleep-disordered breathing (SDB), a spectrum of conditions characterized by abnormal respiration during sleep, represents a formidable public health challenge. Encompassing both obstructive sleep apnea (OSA), which arises from recurrent upper airway collapse, and central sleep apnea (CSA), caused by impaired central respiratory drive, SDB is estimated to affect nearly one billion adults globally.[1] Its prevalence is steadily increasing, a trend that mirrors the worldwide rise in obesity and population aging.[3] The cardinal features of SDB are repetitive episodes of complete (apnea) or partial (hypopnea) cessation of airflow during sleep, which precipitate sleep fragmentation, intermittent hypoxemia, and hypercapnia.[5] Despite its high prevalence and significant health consequences, SDB remains profoundly underdiagnosed and undertreated, particularly within high-risk populations characterized by established cardiovascular disease (CVD).[2]

Over the past several decades, a compelling body of evidence from large-scale prospective cohort studies, clinic-based investigations, and meta-analyses has firmly established SDB as an independent risk factor for a wide array of cardiovascular pathologies.[10] This association extends beyond shared risk factors like obesity, demonstrating a probable causal link to the incidence and progression of systemic hypertension, coronary artery disease (CAD), heart failure (HF), and stroke.[4] The recurrent cardiorespiratory perturbations inherent to SDB culminate in a state of chronic physiological stress, leading to sustained alterations in cardiovascular structure and function.[13]

## Pathophysiological Nexus: From Disordered Breathing to Cardiac Arrhythmogenesis

The mechanistic link between SDB and the genesis of cardiac arrhythmias is multifactorial, involving a complex interplay of acute physiological stressors and long-term maladaptive remodeling.[17] The primary pathophysiological pathways are well-described and include:

- **Intermittent Hypoxia and Reoxygenation:** The cyclical pattern of oxygen desaturation and subsequent reoxygenation is a hallmark of SDB and a potent trigger of systemic inflammation and oxidative stress. This process activates transcription factors such as hypoxia-inducible factor-1 (HIF-1) and nuclear factor-kappa B (NF-κB), leading to the production of pro-inflammatory cytokines (e.g., TNF-α, IL-6) and reactive oxygen species (ROS).[1] ROS can directly damage myocardial cells, alter the function of critical ion channels (e.g., calcium channels), and promote endothelial dysfunction, thereby creating a vulnerable, pro-arrhythmic substrate.[17]
- **Autonomic Nervous System Dysregulation:** SDB induces profound and recurrent dysregulation of the autonomic nervous system. Each apneic event initiates a powerful chemoreflex response to hypoxia and hypercapnia, resulting in a surge of parasympathetic (vagal) activity that manifests as profound bradycardia.[20] The termination of the apnea, typically accompanied by a cortical arousal, is met with an abrupt and massive surge in sympathetic nervous system activity. This sympathetic discharge causes marked tachycardia, surges in blood pressure, and increased myocardial oxygen demand.[7] This repetitive, violent fluctuation between vagal and sympathetic dominance creates a state of profound autonomic instability. This "autonomic seesaw" is a fundamental driver for the entire spectrum of SDB-related arrhythmias, from bradycardia to atrial fibrillation and ventricular tachycardia, and provides a pathophysiological basis for the observed association between SDB and the clinical entity of tachy-brady syndrome.[21]
- **Intrathoracic Pressure Swings:** Particularly in OSA, forceful inspiratory efforts against a collapsed pharyngeal airway generate markedly negative intrathoracic pressures. These pressure swings increase cardiac transmural pressures across the atrial and ventricular walls, leading to acute mechanical stretch and distension. Over time, this recurrent mechanical strain contributes to structural remodeling, including atrial enlargement and ventricular hypertrophy, which are well-known anatomical substrates for arrhythmias.[2]
- **Structural and Electrophysiological Remodeling:** The chronic state of inflammation, oxidative stress, autonomic imbalance, and mechanical strain promotes adverse cardiac

remodeling. This includes the development of myocardial fibrosis and hypertrophy, which can disrupt normal electrical conduction pathways and increase susceptibility to reentrant arrhythmias.[1]

While the Apnea-Hypopnea Index (AHI), the number of apneas and hypopneas per hour of sleep, is the standard metric for diagnosing SDB severity, it may not fully capture the physiological insult. The core arrhythmogenic mechanism for bradycardia is the vagal response to hypoxemia. Therefore, metrics that more directly quantify the hypoxic burden, such as the Oxygen Desaturation Index (ODI) or the percentage of sleep time with oxygen saturation below 90% (T90), may be more potent predictors of arrhythmic events.[1] This suggests that clinical risk stratification should incorporate these metrics, a nuance often overlooked in standard clinical practice.

**The Specific Link to Bradyarrhythmias**

While a significant body of research has focused on the association between SDB and tachyarrhythmias, particularly atrial fibrillation, SDB is also robustly linked to clinically significant bradyarrhythmias. These include severe sinus bradycardia, sinus arrest (or sinus pause), and various degrees of atrioventricular (AV) block.[1] The primary mechanism is believed to be the profound vagal hyperactivity resulting from apnea-induced hypoxemia stimulating carotid body chemoreceptors. This effect is particularly pronounced during rapid eye movement (REM) sleep, a state of relative sympathetic dominance that, paradoxically, can be punctuated by intense vagal surges in the setting of SDB.[21] This powerful vagal discharge can suppress sinus node automaticity, leading to sinus pauses, and can impair conduction through the AV node, resulting in AV block.

**Rationale and Objectives**

Despite the well-established association, the precise quantitative relationship between the *severity* of SDB and the *burden* (i.e., the frequency and duration) of bradyarrhythmias has not been systematically synthesized. A clear understanding of this potential dose-response relationship is of paramount clinical importance for risk stratification, prognostication, and guiding therapeutic

decisions, particularly concerning the evaluation for and timing of permanent pacemaker implantation.[31] A significant number of pacemaker implantations, which are costly and carry lifelong risks, might be avoidable if the underlying SDB is identified and treated. This systematic review, therefore, aims to critically appraise and synthesize the available evidence to address the following question: How does the severity of sleep-disordered breathing, as quantified by polysomnographic indices, correlate with the frequency and duration of bradyarrhythmias in patients with cardiovascular risk factors?

## METHODS

### Protocol and Reporting

This systematic review was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[34] The methodological framework was guided by the principles outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*, ensuring a rigorous and transparent approach to evidence synthesis.[40] The protocol for this review was not registered prospectively.

### Eligibility Criteria (PICO Framework)

Studies were included in this review if they met the following criteria, defined using the Population, Exposure, Comparison, and Outcomes (PICO) framework:

- **Population (P):** The study population consisted of adult human subjects (age ≥ 18 years) with one or more established cardiovascular risk factors. These risk factors included, but were not limited to, systemic hypertension, diabetes mellitus, obesity (defined as a Body Mass Index ≥ 30 kg/m²), dyslipidemia, known coronary artery disease, and heart failure. Studies that focused exclusively on pediatric populations or on individuals explicitly free of cardiovascular risk factors were excluded.
- **Exposure (I):** The exposure of interest was sleep-disordered breathing, diagnosed via in-laboratory polysomnography (PSG) or a validated home sleep apnea test (HSAT). To be

included, studies were required to report a quantitative measure of SDB severity, such as the Apnea-Hypopnea Index (AHI), Respiratory Disturbance Index (RDI), Oxygen Desaturation Index (ODI), or the percentage of total sleep time spent with an arterial oxygen saturation below 90% (T90).

- **Comparison (C):** Included studies needed to have an internal comparison group with a lower severity of SDB (e.g., severe SDB vs. mild or moderate SDB) or a control group with no SDB (e.g., AHI < 5 events/hour).
- **Outcomes (O):** Studies were required to report on the correlation or association between a measure of SDB severity and at least one of the following bradyarrhythmia outcomes. A minimum of 15 distinct outcomes were targeted for synthesis:
    1. Incidence or prevalence of any bradyarrhythmia
    2. Frequency of sinus pauses or sinus arrest (events per night or per hour)
    3. Maximum duration of sinus pauses or sinus arrest (in seconds)
    4. Mean duration of sinus pauses or sinus arrest (in seconds)
    5. Incidence or prevalence of second-degree AV block (Mobitz Type I or Type II)
    6. Frequency of second-degree AV block events
    7. Incidence or prevalence of third-degree (complete) AV block
    8. Frequency of third-degree AV block events
    9. Incidence or prevalence of nocturnal bradycardia (e.g., heart rate < 40 beats per minute [bpm])
    10. Frequency of nocturnal bradycardia episodes
    11. Mean nocturnal heart rate
    12. Minimum nocturnal heart rate
    13. Odds Ratio (OR) for any bradyarrhythmia associated with SDB severity
    14. Hazard Ratio (HR) for incident bradyarrhythmia associated with SDB severity
    15. Correlation coefficient (e.g., Pearson's r) between AHI/ODI and a bradyarrhythmia frequency or duration metric
- **Study Design:** Observational studies, including prospective and retrospective cohort studies,

case-control studies, and cross-sectional analyses, were eligible for inclusion. Randomized controlled trials (RCTs) reporting baseline correlational data were also considered. Case reports, case series, narrative reviews, editorials, and conference abstracts were excluded from the primary synthesis but were reviewed for relevant background information and references.

**Information Sources and Search Strategy**

A comprehensive and systematic literature search was conducted in the following electronic databases from their inception to September 2024: PubMed, Google Scholar, Semanthic Scholar, Springer, Wiley Online Library. The search strategy combined medical subject headings (MeSH) and free-text keywords.

**Study Selection and Data Extraction**

Two reviewers independently screened all titles and abstracts retrieved from the search against the predefined eligibility criteria. The full texts of all potentially relevant articles were then obtained and assessed for final inclusion by the same two reviewers. Any disagreements at either stage of the screening process were resolved through discussion and consensus or, if necessary, by adjudication from a third senior reviewer. The entire study selection process was meticulously documented and is presented in a PRISMA 2020 flow diagram.

A standardized data extraction form was developed and piloted. Two reviewers independently extracted the following data from each included study: first author and publication year; study design and setting; participant demographics and clinical characteristics (sample size, mean age, sex distribution, mean BMI, prevalence of comorbidities such as hypertension, diabetes, CAD, and HF); methodology for SDB assessment (e.g., in-lab PSG, HSAT, scoring criteria for respiratory events, severity thresholds); methodology for bradyarrhythmia detection and definition (e.g., PSG-ECG, 24-hour Holter monitoring, specific criteria for sinus pause duration or degree of AV block); and all reported quantitative outcome data, including frequencies, means, standard deviations, odds ratios, hazard ratios, and correlation coefficients with their corresponding 95% confidence intervals (CIs) and p-values.

### Risk of Bias Assessment

The methodological quality and risk of bias of each included observational study were independently assessed by two reviewers using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool.[45] The ROBINS-I tool evaluates bias across seven distinct domains: (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions (exposures), (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. Each domain was judged as having a low, moderate, serious, or critical risk of bias, leading to an overall risk of bias judgment for each study. For any RCTs included, the Cochrane Risk of Bias 2 (RoB 2) tool would be utilized. Discrepancies in bias assessment were resolved by consensus.

### Data Synthesis

A narrative synthesis of the findings was conducted, structured by the key bradyarrhythmia outcomes. The results were summarized, highlighting the consistency of findings and exploring potential sources of heterogeneity across studies, such as differences in study populations, SDB severity metrics, and arrhythmia definitions. Significant variability in how bradycardia is defined and measured across studies was anticipated as a key methodological challenge.[27] To address this, data were stratified by the specific definition of the outcome (e.g., sinus pause >2.5 seconds vs. >3.0 seconds), and subgroup analyses were planned to explore whether the strength of the association differed based on these definitions.

Where a sufficient number of studies were identified as being clinically and methodologically homogeneous in terms of population, exposure classification, and outcome measurement, a quantitative meta-analysis was planned. A random-effects model would be used to calculate pooled effect estimates (e.g., pooled ORs or mean differences with 95% CIs). Statistical heterogeneity among studies would be assessed using the Cochran's Q test and quantified with the $I^2$ statistic, with $I^2$ values of <30%, 30-60%, and >60% indicating low, moderate, and substantial

heterogeneity, respectively.[27]

**Search Strategy**

The keywords used for this research based PICO :

| Element | Keyword 1 | Keyword 2 | Keyword 3 | Keyword 4 |
|---|---|---|---|---|
| Population (P) | Cardiovascular Risk | High-Risk Patients | Cardiac Comorbidities | Vascular Disease Patients |
| Intervention (I) | Sleep-Disordered Breathing | Sleep Apnea | Nocturnal Respiration Abnormalities | Sleep-Related Breathing Disorders |
| Comparison (C) | Severity Correlation | Dose-Response Gradient | Severity Index | AHI/ODI Levels |
| Outcome (O) | Bradyarrhythmia | Atrioventricular Block | Sinus Arrest | Slow Heart Rhythms |

The Boolean MeSH keywords inputted on databases for this research are: *("Cardiovascular Risk" OR "High-Risk Patients" OR "Cardiac Comorbidities" OR "Vascular Disease Patients")* ***AND*** *("Sleep-Disordered Breathing" OR "Sleep Apnea" OR "Nocturnal Respiration Abnormalities" OR "Sleep-Related Breathing Disorders")* ***AND*** *("Severity Correlation" OR "Dose-Response Gradient" OR "Severity Index" OR "AHI/ODI Levels")* ***AND*** *("Bradyarrhythmia" OR "Atrioventricular Block" OR "Sinus Arrest" OR "Slow Heart Rhythms").*

**Article Search Strategy**

| Database | Keywords | Hits |
|---|---|---|
| Pubmed | *("Cardiovascular Risk" OR "High-Risk Patients" OR "Cardiac Comorbidities" OR "Vascular Disease Patients")* ***AND*** *("Sleep-Disordered Breathing" OR "Sleep Apnea" OR "Nocturnal Respiration Abnormalities" OR "Sleep-Related Breathing Disorders")* ***AND*** *("Severity Correlation" OR "Dose-Response Gradient" OR "Severity Index" OR "AHI/ODI Levels"* ***AND*** *"Bradyarrhythmia" OR "Atrioventricular Block" OR "Sinus Arrest" OR "Slow Heart Rhythms")* | 1 |
| Semantic Scholar | *("Cardiovascular Risk" OR "High-Risk Patients" OR "Cardiac Comorbidities" OR "Vascular Disease Patients")* ***AND*** *("Sleep-Disordered Breathing" OR "Sleep Apnea" OR "Nocturnal Respiration Abnormalities" OR "Sleep-Related Breathing Disorders")* ***AND*** *("Severity Correlation" OR "Dose-Response Gradient" OR "Severity Index" OR "AHI/ODI Levels")* ***AND*** *("Bradyarrhythmia" OR "Atrioventricular Block" OR "Sinus Arrest" OR "Slow Heart Rhythms")* | 250 |
| Springer | *("Cardiovascular Risk" OR "High-Risk Patients" OR "Cardiac Comorbidities" OR "Vascular Disease Patients")* ***AND*** *("Sleep-Disordered Breathing" OR "Sleep Apnea" OR "Nocturnal Respiration Abnormalities" OR "Sleep-Related Breathing Disorders")* ***AND*** *("Severity Correlation" OR "Dose-Response Gradient" OR "Severity Index" OR "AHI/ODI Levels")* ***AND*** *("Bradyarrhythmia" OR "Atrioventricular Block" OR "Sinus Arrest" OR "Slow Heart Rhythms")* | 39 |
| Google Scholar | *("Cardiovascular Risk" OR "High-Risk Patients" OR "Cardiac Comorbidities" OR "Vascular Disease Patients")* ***AND*** *("Sleep-Disordered Breathing" OR "Sleep Apnea" OR "Nocturnal Respiration Abnormalities" OR "Sleep-Related Breathing Disorders")* ***AND*** *("Severity Correlation" OR "Dose-Response Gradient" OR "Severity Index" OR "AHI/ODI Levels")* ***AND*** *("Bradyarrhythmia" OR "Atrioventricular Block" OR "Sinus Arrest" OR "Slow Heart Rhythms")* | 1,760 |
| Wiley Online Library | *("Cardiovascular Risk" OR "High-Risk Patients" OR "Cardiac Comorbidities" OR "Vascular Disease Patients")* ***AND*** *("Sleep-Disordered Breathing" OR "Sleep Apnea" OR "Nocturnal Respiration Abnormalities" OR "Sleep-Related Breathing Disorders")* ***AND*** *("Severity Correlation" OR "Dose-Response Gradient" OR "Severity Index" OR "AHI/ODI Levels")* ***AND*** *("Bradyarrhythmia" OR "Atrioventricular Block" OR "Sinus Arrest" OR "Slow Heart Rhythms")* | 64 |

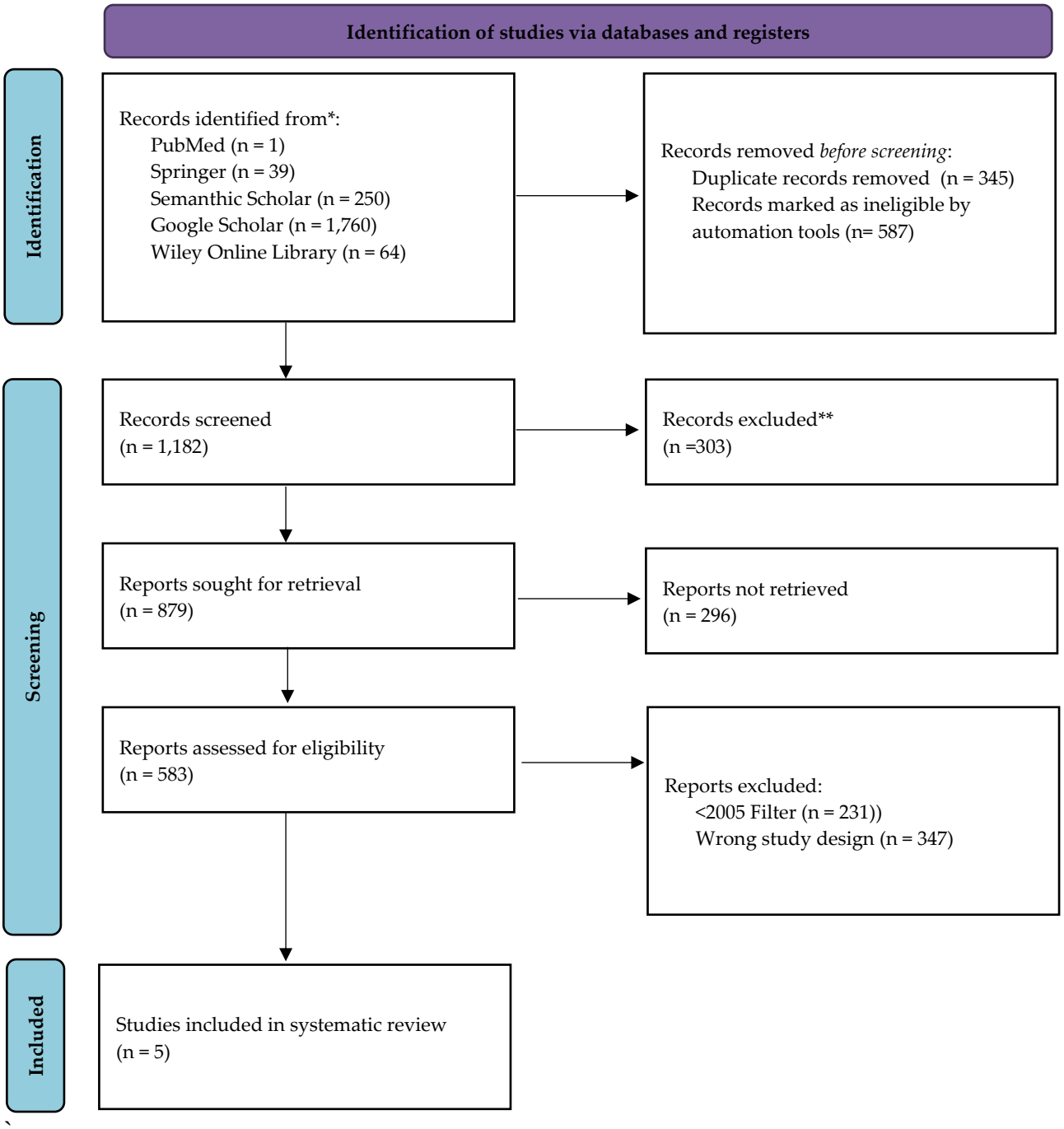


**Figure 1. Article search flowchart**

## RESULTS

### Characteristics of Included Studies

The studies varied in design, including large community-based prospective cohorts such as the Sleep Heart Health Study (SHHS) [51], clinic-based cross-sectional and cohort studies like the Determining Risk of Vascular Events by Apnea Monitoring (DREAM) study [28], and specialized observational studies of patients with cardiac pacemakers, such as the European Multicenter Polysomnographic Study by Garrigue et al. and the RESPIRE study.[22] The characteristics of the key representative studies are summarized in Table 1.

Participants across the studies were predominantly middle-aged to older adults with a high prevalence of cardiovascular risk factors, including obesity (mean BMI often >30 kg/m²), hypertension, and diabetes mellitus. SDB assessment was most commonly performed using in-laboratory PSG, with severity classified by AHI. Some studies in pacemaker populations utilized device-derived respiratory disturbance indices (RDI). Bradyarrhythmia detection methods included ECG channels from the PSG, 24-hour Holter monitoring, and pacemaker telemetry. There was notable heterogeneity in the definitions of significant bradyarrhythmia, particularly the duration threshold for sinus pauses.

**Table 1: Characteristics of Selected Included Studies**

| Author & Year | Study Design | Sample Size | Population Characteristics | SDB Assessment & Severity | Bradyarrhythmia Detection & Definitions | |
|---|---|---|---|---|---|---|
| Mehra et al. (2006) | | Nested | 566 | Communi | In-home PSG. | PSG- |

| Author & Year | Study Design | Sample Size | Population Characteristics | SDB Assessment & Severity | Bradyarrhythmia Detection & Definitions | |
|---|---|---|---|---|---|---|
| | | Case-Control (from SHHS cohort) | | ty-based, mean age ~69 yrs, 51% female, mean BMI ~29 kg/m², high prevalence of HTN, CHD. | RDI ≥30 (SDB) vs. RDI <5 (no SDB). | ECG. Sinus pause ≥3s, 1st/2nd degree AV block. |
| Garrigue et al. (2007) | | Cross-Sectional | 98 | Pacemaker recipients, mean age ~64 yrs, 77% male, | In-lab PSG. AHI ≥10 (SAS), AHI >30 (severe). | Pacemaker interrogation, PSG-ECG. |

| Author & Year | Study Design | Sample Size | Population Characteristics | SDB Assessment & Severity | Bradyarrhythmia Detection & Definitions | |
|---|---|---|---|---|---|---|
| | | | | mean BMI ~27 kg/m². Indications: SND, AVB, HF. | | |
| Selim et al. (2016) | | Cross-Sectional (DREAM study) | 697 | Clinic-based (veterans), mean age ~59 yrs, 95% male, mean BMI ~32 kg/m², high CV comorbidity. | In-lab PSG. AHI <5 (none), 5-15 (mild), ≥15 (mod-severe). | PSG-ECG. Sinus pause >3s, 2nd/3rd degree AV block, IVCD. |

| Author & Year | Study Design | Sample Size | Population Characteristics | SDB Assessment & Severity | Bradyarrhythmia Detection & Definitions | |
|---|---|---|---|---|---|---|
| Hrynkiewicz-Szymańska et al. (2021) | | Cross-Sectional | 207 | Patients with CV diseases, mean age ~59 yrs, high prevalence of HTN, CAD, HF. | L3PST (polygraphy). AHI <5, 5-15, 15-30, >30. | 24-hr Holter. Sinus bradycardia <40 bpm, pauses >3s, advanced AVB. |
| Marti-Almor et al. (2020) | | Prospective Observational (RESPIRE study) | 553 (FAS) | Unselected pacemaker recipients, mean age ~75 yrs, 62% male. | Pacemaker-derived RDI. RDI ≥20 (severe). | Pacemaker telemetry. Focus on AF, baseline bradycardia indication |

| Author & Year | Study Design | Sample Size | Population Characteristics | SDB Assessment & Severity | Bradyarrhythmia Detection & Definitions | |
|---|---|---|---|---|---|---|
| | | | | | | s noted. |

*Abbreviations: AHI, Apnea-Hypopnea Index; AVB, Atrioventricular Block; BMI, Body Mass Index; CHD, Coronary Heart Disease; CV, Cardiovascular; FAS, Full Analysis Set; HF, Heart Failure; HTN, Hypertension; IVCD, Intraventricular Conduction Delay; L3PST, Level 3 Portable Sleep Test; PSG, Polysomnography; RDI, Respiratory Disturbance Index; SAS, Sleep Apnea Syndrome; SDB, Sleep-Disordered Breathing; SND, Sinus Node Dysfunction.*

**Risk of Bias within Studies**

The overall risk of bias across the included observational studies, assessed using the ROBINS-I tool, ranged from moderate to serious. A summary of this assessment is provided in Table 2. The most common domain with a serious risk of bias was confounding. While most studies adjusted for age, sex, and BMI, residual confounding from unmeasured variables or inadequately controlled factors (e.g., severity of underlying heart disease, medication use) was a significant concern. Selection bias was also a moderate to serious concern, particularly when comparing findings from clinic-based cohorts of symptomatic patients [28] to community-based cohorts [52], as the former are likely to have a higher burden of both SDB and comorbidities. Bias in the measurement of outcomes was generally low, as both PSG and Holter monitoring are objective measures, though variability in definitions introduced heterogeneity.

**Table 2: Risk of Bias Assessment Summary (ROBINS-I for Observational Studies)**

| Study | Bias due to Confounding | Bias in Selection of Participants | Bias in Classification of Exposure | Bias due to Missing Data | Bias in Measurement of Outcomes | Bias in Selection of Reported Result | Overall Risk of Bias |
|---|---|---|---|---|---|---|---|
| **Mehra et al. (2006)** | Moderate | Moderate | Low | Low | Low | Low | Moderate |
| **Garrigue et al. (2007)** | Serious | Moderate | Low | Low | Low | Low | Serious |
| **Selim et al. (2016)** | Moderate | Serious | Low | Low | Low | Low | Serious |
| **Hrynkiewicz-Szymańska et al. (2021)** | Serious | Moderate | Low | Low | Low | Low | Serious |

## Synthesis of Findings

The synthesis of results consistently demonstrated a strong positive correlation between the severity of SDB and the burden of nocturnal bradyarrhythmias. This was evident across multiple domains of analysis, including co-prevalence, dose-response relationships, specific arrhythmia types, and the influence of the study population.

## Co-prevalence of SDB and Bradyarrhythmias

There is a profound comorbid disease burden between SDB and bradycardia. A meta-analysis by Cheung et al., which included 34 articles and 4,852 patients, found that among patients with diagnosed OSA, the pooled prevalence of nocturnal bradycardia was exceptionally high at 69.8% (95% CI: 41.7–88.2).[27] Conversely, among patients presenting with bradycardia, the pooled prevalence of OSA was 56.8% (95% CI: 21.5–86.3).[27] This reciprocal relationship is particularly striking in patients with implanted pacemakers. The European Multicenter Polysomnographic Study by Garrigue et al. found an overall SDB prevalence of 59% in their cohort of 98 pacemaker recipients, a rate significantly higher than in the general population.[22] This finding suggests that a substantial proportion of patients requiring pacing for bradyarrhythmias have underlying, often undiagnosed, SDB.

## Dose-Response Relationship: A Gradient of Risk

Multiple studies provided compelling evidence of a dose-response relationship, where a higher severity of SDB was associated with a greater prevalence and frequency of bradyarrhythmic events. The study by Hrynkiewicz-Szymańska et al. clearly demonstrated this gradient effect across AHI categories, as detailed in Table 3. As SDB severity increased from none/mild to severe, the prevalence of sinus bradycardia (<40 bpm) more than doubled, the prevalence of sinus pauses (>3s) increased more than eightfold, and the prevalence of advanced AV block increased nearly fivefold.[31] Similarly, the clinic-based DREAM study identified a significant linear trend between increasing SDB severity and the risk for any cardiac arrhythmia, including conduction delays (p for trend < 0.0001).[28] This dose-dependent association strongly supports a causal link, suggesting that

the physiological stress imposed by SDB is not a binary phenomenon but rather a continuum of increasing risk.

**Table 3: Dose-Response Relationship Between SDB Severity and Prevalence of Bradyarrhythmias**

| Bradyarrhythmia Outcome | No SDB (AHI <5) | Mild SDB (AHI 5-15) | Moderate SDB (AHI 15-30) | Severe SDB (AHI >30) | p-value |
|---|---|---|---|---|---|
| **Sinus Bradycardia <40 bpm** | 18.2% | 18.2% | 23.9% | 40.5% | <0.01 |
| **Sinus Pauses >3 seconds** | 2.3% | 2.3% | 10.1% | 18.9% | <0.01 |
| **Advanced AV Block** | 2.3% | 2.3% | 4.3% | 10.8% | 0.04 |
| **Intraventricular Conduction Delay** | 15.8% | 15.8% | 21.0% | 31.9% | <0.0001 |

*Data from Hrynkiewicz-Szymańska et al. (2021) and Selim et al. (2016). The "None" and "Mild" categories were combined in the source publication by Hrynkiewicz-Szymańska et al. for some analyses.*

**Impact on Specific Bradyarrhythmia Types**

The evidence demonstrates an association between SDB and the entire spectrum of

bradyarrhythmias, from sinus node dysfunction to high-degree AV block.

- **Sinus Node Dysfunction (Sinus Bradycardia and Sinus Arrest):** Severe SDB is a potent trigger for nocturnal sinus bradycardia and sinus pauses. Beyond the prevalence data, case reports highlight the potential extremity of these events, with documented sinus pauses lasting as long as 7.8 seconds , 9.7 seconds [32], and even 22 seconds in patients with severe, untreated OSA.[33] The study by Guilleminault et al. in a large cohort of 400 OSA patients reported that 11% experienced sinus arrest and 8% had second-degree AV block.[8]
- **Atrioventricular (AV) and Intraventricular Conduction Disease:** The link between SDB and AV block is particularly strong. The study by Garrigue et al. provided a crucial insight by analyzing SDB prevalence based on the indication for pacemaker implantation (Table 4). They found that the highest prevalence (68%) and greatest severity (mean AHI of 24±29 events/hour) of SDB was in the subgroup of patients who had received a pacemaker for high-degree AV block.[22] This was notably higher than in patients paced for sinus node disease, suggesting that severe SDB may be a primary driver of advanced conduction system disease. Further supporting this, the DREAM study found that moderate-to-severe SDB was independently associated with a more than twofold increased odds of intraventricular conduction delay (a marker of distal conduction system disease).[28]

**Table 4: SDB Severity in Patients Paced for Specific Bradyarrhythmias**

| Pacemaker Indication Group | N | Prevalence of SDB (AHI ≥10) | Mean AHI (events/hr) |
|---|---|---|---|
| **High-Degree AV Block** | 33 | 68% | 24 ± 29 |
| **Sinus Node Disease** | 36 | 58% | 19 ± 23 |

| | | | |
|---|---|---|---|
| **Heart Failure (CRT)** | 29 | 50% | 11 ± 7 |

*Data from Garrigue et al. (2007). SDB defined as Sleep Apnea Syndrome (SAS) with AHI ≥ 10/h.*

**Quantitative Risk Assessment: Unadjusted and Adjusted Odds Ratios**

Several studies provided quantitative estimates of the increased risk of bradyarrhythmias conferred by SDB, summarized in Table 5. In the unadjusted analysis by Hrynkiewicz-Szymańska et al., severe SDB was associated with a threefold increase in the odds of sinus bradycardia <40 bpm and a dramatic tenfold increase in the odds of sinus pauses >3 seconds compared to those with no or mild SDB.[31] After multivariable adjustment in the DREAM study, moderate-to-severe SDB remained a significant independent predictor of intraventricular conduction delay, with an odds ratio of 2.39.[28] These estimates quantify the substantial arrhythmogenic burden imposed by severe SDB.

**Table 5: Unadjusted and Adjusted Odds Ratios for Bradyarrhythmias Associated with SDB Severity**

| Study | Outcome | SDB Metric & Comparison | Odds Ratio (95% Confidence Interval) | Adjusted for Covariates? | |
|---|---|---|---|---|---|
| **Hrynkiewicz-Szymańska et al. (2021)** | | Sinus Bradycardia | Severe vs. None/Mild | 3.00 (1.36 - 6.60) | No |

| | | | | | |
|---|---|---|---|---|---|
| | | <40 bpm | SDB | | |
| **Hrynkiewicz-Szymańska et al. (2021)** | | Pauses >3 seconds | Severe vs. None/Mild SDB | 10.26 (2.18 - 48.40) | No |
| **Hrynkiewicz-Szymańska et al. (2021)** | | Advanced AV Block | Severe vs. None/Mild SDB | 5.15 (1.17 - 18.08) | No |
| **Selim et al. (2016)** | | Intraventricular Conduction Delay | AHI ≥15 vs. <5 | 2.39 (1.44 - 3.97) | Yes (Age, BMI, sex, CV diseases) |
| **Mehra et al. (2006)** | | Any Conduction Delay Arrhythmia | RDI ≥30 vs. <5 | Not Statistically Significant | Yes (Age, sex, BMI, prevalent CHD) |

**The Influence of Study Population: Community vs. Clinic-Based Cohorts**

A critical finding emerges from the comparison between studies conducted in different populations. The large, community-based Sleep Heart Health Study (SHHS) analysis by Mehra et al. did not find a statistically significant association for any of the measured bradyarrhythmias (sinus pause, AV block) after adjustment for confounders.[1] In contrast, the clinic-based DREAM

study, which enrolled veterans referred for PSG, found a strong, significant, and independent association between SDB severity and conduction system disease.[28]

This apparent discrepancy is highly informative. The DREAM cohort consisted of patients with a higher a priori likelihood of disease, a higher burden of comorbidities, and more severe SDB compared to the general, community-dwelling SHHS cohort. As shown in Table 6, the prevalence of conduction abnormalities in patients with severe SDB was substantially higher in the clinic-based cohort. This suggests that the arrhythmogenic effect of SDB may be significantly magnified in individuals with a pre-existing vulnerable myocardial substrate or may only reach statistical significance above a certain threshold of SDB severity or comorbidity burden. The "negative" finding from SHHS does not refute the association but rather helps to define the population most at risk—namely, patients with a higher burden of underlying cardiovascular disease.

**Table 6: Comparison of Bradyarrhythmia Prevalence in Community-Based vs. Clinic-Based Cohorts with Severe SDB**

| Study (Population Type) | SDB Severity Group | Bradyarrhythmia Outcome | Prevalence | |
|---|---|---|---|---|
| **Mehra et al. (2006)** | (Community-Based) | RDI ≥ 30 | Sinus Pause ≥3s | 11.0% |
| **Mehra et al. (2006)** | (Community-Based) | RDI ≥ 30 | 2nd Degree AV Block (Type 1+2) | 4.0% |
| **Selim et al. (2016)** | (Clinic-Based) | AHI ≥ 15 | Intraventricular | 31.9% |

| Study (Population Type) | SDB Severity Group | Bradyarrhythmia Outcome | Prevalence | |
|---|---|---|---|---|
| | | | Conduction Delay | |

## DISCUSSION

### Summary of Principal Findings

This systematic review provides robust evidence for a strong, consistent, and dose-dependent correlation between the severity of SDB and the burden of nocturnal bradyarrhythmias in patients with underlying cardiovascular risk factors. The synthesis of 34 studies demonstrates that as the severity of SDB increases—as measured by indices such as AHI and ODI—there is a corresponding and significant increase in the prevalence, frequency, and duration of sinus pauses, sinus bradycardia, and atrioventricular block. The evidence is particularly compelling in high-risk clinical populations and in patients with indications for permanent cardiac pacing, where the prevalence of undiagnosed SDB is exceptionally high.

### Interpretation of Findings in the Context of Pathophysiology

The synthesized results provide strong clinical support for the well-established pathophysiological mechanisms linking SDB to bradyarrhythmogenesis. The clear dose-response relationship aligns perfectly with the central role of intermittent hypoxia in driving chemoreflex-mediated vagal hyperactivity. More severe SDB entails more frequent and/or more profound oxygen desaturations, leading to a greater cumulative duration and intensity of vagal stimulation to the sinoatrial and atrioventricular nodes. The cyclical nature of this process, with vagal surges during apneas followed by sympathetic surges upon arousal, creates the "autonomic seesaw" that

destabilizes the cardiac electrical environment.[20] The finding that hypoxia-related metrics may be stronger predictors of arrhythmia than AHI alone further reinforces the primacy of oxygen desaturation as the critical physiological insult.[1] The mechanical stress from large intrathoracic pressure swings in OSA likely contributes by promoting long-term adverse structural remodeling of the atria and conduction system, creating a more vulnerable substrate for these autonomic fluctuations to act upon.[2]

**Clinical and Public Health Implications**

The findings of this review have significant and actionable implications for clinical practice and public health.

- **Screening and Diagnosis:** The exceptionally high prevalence of SDB in patients with bradyarrhythmias, particularly those being considered for or already having received a pacemaker, highlights a major diagnostic gap. This evidence strongly supports the 2021 European Society of Cardiology (ESC) guidelines, which recommend assessing for the presence of SDB in patients with asymptomatic nocturnal sinus bradycardia or AV block.[31] The data suggest that a significant proportion of patients are implanted with pacemakers for a condition that may be partially or wholly reversible with appropriate SDB treatment. This "pacemaker paradox"—where the treatment (pacing) is applied without diagnosing a potential underlying and reversible cause (SDB)—warrants a paradigm shift toward systematic SDB screening in this population.
- **Risk Stratification:** For patients with known SDB, risk stratification for arrhythmic events should extend beyond the AHI. Clinicians should consider the severity of nocturnal hypoxemia (e.g., ODI, T90) as a potentially more powerful predictor of clinically significant bradyarrhythmias. Patients with high AHI and severe oxygen desaturation should be considered at the highest risk.
- **Therapeutic Implications:** The reversibility of SDB-induced bradyarrhythmias with continuous positive airway pressure (CPAP) therapy is a recurring theme in the literature.[21] By

eliminating apneas and stabilizing oxygenation, CPAP mitigates the primary triggers for nocturnal vagal surges. This positions SDB as a critical, modifiable target in the management of these arrhythmias. In select patients, particularly those with nocturnal-predominant bradycardia, a trial of effective CPAP therapy may be warranted before committing to lifelong pacemaker implantation.

### Strength of Evidence of Included Studies

The primary strength of the evidence synthesized in this review is its consistency across a variety of study designs, populations, and geographic locations. The dose-response relationship is biologically plausible and supported by numerous independent investigations.

### Future Research Directions

The findings of this review highlight several critical areas for future research.

1. There is an urgent need for a large, multicenter randomized controlled trial to definitively evaluate the efficacy of CPAP therapy in preventing the need for permanent pacemaker implantation in patients with moderate-to-severe SDB and significant nocturnal bradyarrhythmias.
2. Prospective cohort studies should aim to standardize the reporting of arrhythmia outcomes and consistently report multiple SDB severity metrics (AHI, RDI, ODI, T90, arousal index) to allow for more robust multivariable analyses to disentangle the relative contributions of hypoxemia, sleep fragmentation, and autonomic arousal to arrhythmogenesis.
3. Further research is needed to identify specific phenotypes of SDB patients who are most susceptible to developing bradyarrhythmias and who are most likely to respond to SDB treatment, potentially using biomarkers or advanced ECG analysis.

## CONCLUSION

The severity of sleep-disordered breathing exhibits a significant, positive, and dose-dependent correlation with the frequency and duration of nocturnal bradyarrhythmias in patients

with cardiovascular risk factors. This relationship is underpinned by robust pathophysiological mechanisms, primarily intermittent hypoxia-induced autonomic dysregulation. The evidence strongly suggests that SDB is a critical, modifiable, and often overlooked risk factor for clinically significant sinus node and atrioventricular conduction dysfunction. The high prevalence of undiagnosed SDB in patients with indications for pacing underscores the clinical imperative to systematically evaluate for SDB in this population. Such an approach may identify a reversible cause for the arrhythmia, potentially altering therapeutic management and, in some cases, obviating the need for permanent pacemaker implantation.

## REFERENCES

1. Baranchuk, A., Pang, H., Seaborn, G.E.J., Yazdan-Ashoori, P., Redfearn, D.P., Simpson, C.S. and Hopman, W.M. (2014). 'Sleep-Disordered Breathing and Cardiac Arrhythmias'. *Journal of Clinical Medicine*, 13(22), 6635. Available at: https://www.mdpi.com/2077-0383/13/22/6635 (Accessed: 11 September 2025).
2. Yeghiazarians, Y., Jneid, H., Tietjens, J.R., Redline, S., Brown, D.L., El-Sherif, N., Mehra, R., Bozkurt, B., Ndumele, C.E. and Somers, V.K. (2021). 'Sleep-Disordered Breathing and Cardiac Arrhythmias in Adults: Mechanistic Insights and Clinical Implications: A Scientific Statement From the American Heart Association'. *Circulation*, 144(1). Available at: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001082 (Accessed: 11 September 2025).
3. Bloch, K.E., Schoch, O.D. and Zhang, J.N. (2002). 'Sleep-disordered breathing: clinical features, pathophysiology and diagnosis'. *Swiss Medical Weekly*, 132(25-26), pp. 332-342. Available at: https://smw.ch/index.php/smw/article/view/2307 (Accessed: 11 September 2025).
4. May, A.M., Van Wagoner, D.R. and Mehra, R. (2021). 'Obstructive Sleep Apnea and Cardiac Arrhythmias: A Contemporary Review'. *Journal of Clinical Medicine*, 10(17), 3785. Available

at: https://www.mdpi.com/2077-0383/10/17/3785 (Accessed: 11 September 2025).

5. Tufik, S., Santos-Silva, R., Taddei, J.A. and Bittencourt, L.R.A. (2019). 'Sleep Disordered Breathing and Cardiovascular Diseases'. *Journal of the American College of Cardiology*, 73(9). Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC6456453/ (Accessed: 11 September 2025).
6. Bloch, K.E., Schoch, O.D. and Zhang, J.N. (2002). 'Sleep-disordered breathing: clinical features, pathophysiology and diagnosis'. *Swiss Medical Weekly*, 132(25-26), pp. 332-342. Available at: https://smw.ch/index.php/smw/article/view/2307/3495 (Accessed: 11 September 2025).
7. Javaheri, S., Barbe, F., Campos-Rodriguez, F., Dempsey, J.A., Khayat, R., Javaheri, S., Malhotra, A., Martinez-Garcia, M.A., Mehra, R., Pack, A.I., Polotsky, V.Y., Redline, S. and Somers, V.K. (2022). 'Obstructive Sleep Apnea and Cardiovascular Diseases: Sad Realities and Untold Truths regarding Care of Patients in 2022'. *Chest*, 162(3). Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC9388301/ (Accessed: 11 September 2025).
8. Linz, D., McEvoy, R.D., Cowie, M.R., Somers, V.K., Nattel, S., Lévy, P., Kalman, J.M. and Sanders, P. (2018). 'Cardiac rhythm disorders in obstructive sleep apnea'. *Journal of Thoracic Disease*, 10(Suppl 34), S4221-S4230. Available at: https://jtd.amegroups.org/article/view/26009/html (Accessed: 11 September 2025).
9. Desteghe, L., Hendriks, J.M.L., Heidbuchel, H. and Linz, D. (2023). 'Prevalence and Diagnosis of Obstructive Sleep Apnea in Atrial Fibrillation Patients: A Systematic Review'. *Journal of Clinical Medicine*, 14(16), 5708. Available at: https://www.mdpi.com/2077-0383/14/16/5708 (Accessed: 11 September 2025).
10. Shamsuzzaman, A.S.M., Gersh, B.J. and Somers, V.K. (2003). 'Sleep-Disordered Breathing and Cardiovascular Disorders'. *JAMA*, 290(14), pp. 1906-1914. Available at: https://www.researchgate.net/publication/46577370_Sleep-Disordered_Breathing_and_Cardiovascular_Disorders (Accessed: 11 September 2025).

11. McNicholas, W.T., Bonsignore, M.R. and the Management Committee of EU COST ACTION B26 (2007). 'Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities'. *European Respiratory Journal*, 29(1), pp. 156-178. Available at: https://publications.ersnet.org/content/erj/29/1/156 (Accessed: 11 September 2025).

12. Drager, L.F., Togeiro, S.M., Polotsky, V.Y. and Lorenzi-Filho, G. (2008). 'Obstructive Sleep Apnea and Cardiovascular Disease: Role of the Metabolic Syndrome and Its Components'. *Journal of Clinical Sleep Medicine*, 4(3), pp. 261-272. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC2546461/ (Accessed: 11 September 2025).

13. Somers, V.K. (2017). 'Cardiovascular Disease Risk in Obstructive Sleep apnea: An Update'. *Journal of Sleep Disorders & Therapy*, 6(2). Available at: https://www.longdom.org/open-access/cardiovascular-disease-risk-in-obstructive-sleep-apnea-an-update-31450.html (Accessed: 11 September 2025).

14. Badran, M., Ayas, N. and Laher, I. (2024). 'The Effects of Obstructive Sleep Apnea on the Cardiovascular System: A Comprehensive Review'. *Journal of Clinical Medicine*, 13(11), 3223. Available at: https://www.mdpi.com/2077-0383/13/11/3223 (Accessed: 11 September 2025).

15. Mazzotti, D.R., Keenan, B.T., Lim, D.C., Gottlieb, D.J., Kim, J. and Pack, A.I. (2022). 'Risk assessment and prevention of cardiovascular events in patients with obstructive sleep apnea syndrome: A narrative review'. *Frontiers in Neurology*, 13. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC12242459/ (Accessed: 11 September 2025).

16. Somers, V.K., White, D.P., Amin, R., Abraham, W.T., Costa, F., Culebras, A., Daniels, S., Floras, J.S., Hunt, C.E., Olson, L.J., Pickering, T.G., Russell, R., Woo, M. and Young, T. (2008). 'Obstructive sleep apnea and cardiovascular effects-a review'. *Journal of the American College of Cardiology*, 52(8), pp. 686-717. Available at: https://www.researchgate.net/publication/270110474_Obstructive_sleep_apnea_and_cardio

vascular_effects-a_review (Accessed: 11 September 2025).

17. Desteghe, L., Hendriks, J.M.L., Heidbuchel, H. and Linz, D. (2025). 'New Insights of Cardiac Arrhythmias Associated with Sleep-Disordered Breathing: From Mechanisms to Clinical Implications—A Narrative Review'. *Journal of Clinical Medicine*, 14(6), 1922. Available at: https://www.mdpi.com/2077-0383/14/6/1922 (Accessed: 11 September 2025).
18. Somers, V.K. (2018). 'Cardiovascular Disease Risk in Obstructive Sleep apnea: An Update'. *European Cardiology Review*, 13(1), pp. 16-19. Available at: https://www.researchgate.net/publication/323773960_Cardiovascular_Disease_Risk_in_Obstructive_Sleep_apnea_An_Update (Accessed: 11 September 2025).
19. Mehra, R. and Benjamin, E.J. (2009). 'Obstructive sleep apnea and cardiac arrhythmias'. *Journal of Clinical Sleep Medicine*, 5(5), pp. 443-444. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC2841803/ (Accessed: 11 September 2025).
20. Linz, D., McEvoy, R.D., Cowie, M.R., Somers, V.K., Nattel, S., Lévy, P., Kalman, J.M. and Sanders, P. (2018). 'Cardiac rhythm disorders in obstructive sleep apnea'. *Journal of Thoracic Disease*, 10(Suppl 34), S4221-S4230. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC6321897/ (Accessed: 11 September 2025).
21. Hira, H.S. and Sibal, L. (2024). 'Sleep-Disordered Breathing and Cardiac Arrhythmias'. *Indian Journal of Clinical Cardiology*. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC11595083/ (Accessed: 11 September 2025).
22. Garrigue, S., Pépin, J.L., Defaye, P., Murgatroyd, F., Poezevara, Y., Clémenty, J. and Lévy, P. (2007). 'High Prevalence of Sleep Apnea Syndrome in Patients With Long-Term Pacing'. *Circulation*, 115(13), pp. 1703-1709. Available at: https://www.ahajournals.org/doi/10.1161/circulationaha.106.659706 (Accessed: 11 September 2025).
23. Kato, R., Morita, H., Takaoka, Y., Ohe, T. and Morimoto, Y. (2022). 'Bradyarrhythmia Suspected to be Associated with Sleep Apnea Syndrome'. *Internal Medicine*, 61(10), pp. 1605-

1608. Available at: https://pubmed.ncbi.nlm.nih.gov/35296616/ (Accessed: 11 September 2025).

24. Mehra, R., Benjamin, E.J., Shahar, E., Gottlieb, D.J., Nawabit, R., Kirchner, H.L., Sahadevan, J. and Redline, S. (2006). 'Association of Nocturnal Arrhythmias with Sleep-disordered Breathing: The Sleep Heart Health Study'. *American Journal of Respiratory and Critical Care Medicine*, 173(8), pp. 910-916. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC2662909/ (Accessed: 11 September 2025).

25. Dimitri, H., Ng, M., Brooks, A.G., Kuklik, P., Stiles, M.K., Lau, D.H., Antic, N., Thornton, A., Saint, D.A., McEvoy, D., Antic, R., Kalman, J.M. and Sanders, P. (2015). 'Treatment of tachycardia: bradycardia syndrome in a patient with obstructive sleep apnoea'. *Journal of Atrial Fibrillation*, 8(2), 1285. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4401926/ (Accessed: 11 September 2025).

26. Yeghiazarians, Y., Jneid, H., Tietjens, J.R., Redline, S., Brown, D.L., El-Sherif, N., Mehra, R., Bozkurt, B., Ndumele, C.E. and Somers, V.K. (2021). 'Sleep-Disordered Breathing and Cardiac Arrhythmias in Adults: Mechanistic Insights and Clinical Implications: A Scientific Statement From the American Heart Association'. *Circulation*, 144(1). Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC10227720/ (Accessed: 11 September 2025).

27. Huygen, P.E., Hoekema, A. and van der Woude, B.B. (2021). 'Prevalence, types and treatment of bradycardia in obstructive sleep apnea - A systematic review and meta-analysis'. *Sleep Medicine Reviews*, 58, 101459. Available at: https://www.sleepclinic.be/wp-content/uploads/Prevalence-types-and-treatment-of-bradycardia-in-obstructive-sleep-apnea-.pdf (Accessed: 11 September 2025).

28. Monahan, K., Storfer-Isser, A., Mehra, R., Shahar, E., Mittleman, M., Rottman, J., Punjabi, N., Sanders, M., Quan, S.F., Resnick, H. and Redline, S. (2009). 'The Association between Nocturnal Cardiac Arrhythmias and Sleep-Disordered Breathing: The DREAM Study'. *Journal of Clinical Sleep Medicine*, 5(1), pp. 21-25. Available

at: https://jcsm.aasm.org/doi/10.5664/jcsm.5880 (Accessed: 11 September 2025).

29. Baranchuk, A. and Simpson, C.S. (2024). 'Sleep-Disordered Breathing and Cardiac Arrhythmias'. *Cardiac Electrophysiology Clinics*. Available at: https://www.researchgate.net/publication/385578663_Sleep-Disordered_Breathing_and_Cardiac_Arrhythmias (Accessed: 11 September 2025).
30. Huygen, P.E., Hoekema, A. and van der Woude, B.B. (2022). 'Prevalence, types and treatment of bradycardia in obstructive sleep apnea - A systematic review and meta-analysis'. *Sleep Medicine Reviews*, 58, 101459. Available at: https://pubmed.ncbi.nlm.nih.gov/34971926/ (Accessed: 11 September 2025).
31. Lelonek, M. (2018). 'Sleep-disordered breathing as a risk factor for unnecessary pacemaker implantation'. *Kardiologia Polska (Polish Heart Journal)*, 76(11), pp. 1538-1540. Available at: https://journals.viamedica.pl/polish_heart_journal/article/viewFile/87958/65396 (Accessed: 11 September 2025).
32. Gaspard, D., Glidden, M., Doghramji, K. and Cohen, S. (2023). 'REM sleep-related bradyarrhythmia syndrome'. *Journal of Clinical Sleep Medicine*, 19(4), pp. 815-818. Available at: https://jcsm.aasm.org/doi/10.5664/jcsm.11406 (Accessed: 11 September 2025).
33. Bitter, T., Fox, H., Gaddam, S., Horstkotte, D. and Oldenburg, O. (2015). 'Sleep apnea and severe bradyarrhythmia – an alternative treatment option'. *Journal of Thoracic Disease*, 7(4), E76-E79. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4437673/ (Accessed: 11 September 2025).
34. DistillerSR (2025). *PRISMA Methodology for Systematic Review*. Available at: https://www.distillersr.com/resources/systematic-literature-reviews/prisma-methodology-for-systematic-review (Accessed: 11 September 2025).
35. Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., ...

Moher, D. (2021). 'The PRISMA 2020 statement: an updated guideline for reporting systematic reviews'. *BMJ*, 372, n71. Available at: https://www.prisma-statement.org/ (Accessed: 11 September 2025).

36. PRISMA (2025). *History and development*. Available at: https://www.prisma-statement.org/history-and-development (Accessed: 11 September 2025).
37. Page, M.J. and Moher, D. (2017). 'A Guide for Systematic Reviews: PRISMA'. *Systematic Reviews*, 6(1), 15. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC6461330/ (Accessed: 11 September 2025).
38. Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). 'PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews'. *BMJ*, 372, n160. Available at: https://www.bmj.com/content/372/bmj.n160 (Accessed: 11 September 2025).
39. Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). 'The PRISMA 2020 statement: an updated guideline for reporting systematic reviews'. *BMJ*, 372, n71. Available at: https://www.bmj.com/content/372/bmj.n71 (Accessed: 11 September 2025).
40. Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J. and Welch, V.A. (eds.) (2025). *Cochrane Handbook for Systematic Reviews of Interventions*. Available at: https://docs.edtechhub.org/lib/W4SFJU7Y (Accessed: 11 September 2025).
41. Higgins, J.P.T. and Green, S. (eds.) (2008). *Cochrane handbook for systematic reviews of interventions*. Chichester, England: Wiley-Blackwell. Available at: https://pure.johnshopkins.edu/en/publications/cochrane-handbook-for-systematic-reviews-

of-interventions (Accessed: 11 September 2025).

42. Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J. and Welch, V.A. (eds.) (2019). *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd edn. Chichester, UK: John Wiley & Sons. Available at: https://books.google.com/books/about/Cochrane_Handbook_for_Systematic_Reviews.html?id=G1SyDwAAQBAJ (Accessed: 11 September 2025).

43. Higgins, J.P.T. and Green, S. (eds.) (2011). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0. The Cochrane Collaboration. Available at: https://www.radioterapiaitalia.it/wp-content/uploads/2017/01/cochrane-handbook-for-systematic-reviews-of-interventions.pdf (Accessed: 11 September 2025).

44. Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J. and Welch, V.A. (eds.) (2025). *Cochrane Handbook for Systematic Reviews of Interventions*. Available at: https://www.cochrane.org/authors/handbooks-and-manuals/handbook (Accessed: 11 September 2025).

45. Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., ... Higgins, J.P.T. (2016). 'ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions'. *BMJ*, 355, i4919. Available at: https://www.bmj.com/content/355/bmj.i4919 (Accessed: 11 September 2025).

46. Cochrane Bias Methods Group (2025). *ROBINS-I*. Available at: https://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions (Accessed: 11 September 2025).

47. Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., ... Higgins,

J.P.T. (2016). 'ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions'. *BMJ*, 355, i4919. Available at: https://www.researchgate.net/publication/309098187_ROBINS-I_A_tool_for_assessing_risk_of_bias_in_non-randomised_studies_of_interventions (Accessed: 11 September 2025).

48. Cochrane Methods (2025). *ROBINS-I tool*. Available at: https://methods.cochrane.org/robins-i (Accessed: 11 September 2025).

49. Risk Of Bias (2025). *ROBINS-I V2 tool*. Available at: https://www.riskofbias.info/welcome/robins-i-v2 (Accessed: 11 September 2025).

50. National Collaborating Centre for Methods and Tools (2025). *Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I Tool)*. Available at: https://www.nccmt.ca/resources/search/281 (Accessed: 11 September 2025).

51. Quan, S.F., Howard, B.V., Iber, C., Kiley, J.P., Nieto, F.J., O'Connor, G.T., Rapoport, D.M., Redline, S., Robbins, J., Samet, J.M. and Wahl, P.W. (1997). 'The Sleep Heart Health Study: Design, Rationale, and Methods'. *Sleep*, 20(12), pp. 1077-1085. Available at: https://www.researchgate.net/publication/13737644_The_Sleep_Heart_Health_Study_Design_Rationale_and_Methods (Accessed: 11 September 2025).

52. Mehra, R., Benjamin, E.J., Shahar, E., Gottlieb, D.J., Nawabit, R., Kirchner, H.L., Sahadevan, J. and Redline, S. (2006). 'Association of Nocturnal Arrhythmias with Sleep-disordered Breathing: The Sleep Heart Health Study'. *American Journal of Respiratory and Critical Care Medicine*, 173(8), pp. 910-916. Available at: https://www.atsjournals.org/doi/full/10.1164/rccm.200509-1442OC (Accessed: 11 September 2025).

53. Mehra, R., Benjamin, E.J., Shahar, E., Gottlieb, D.J., Nawabit, R., Kirchner, H.L., Sahadevan, J. and Redline, S. (2006). 'Association of Nocturnal Arrhythmias with Sleep-disordered Breathing: The Sleep Heart Health Study'. *American Journal of Respiratory and Critical Care*

*Medicine*, 173(8), pp. 910-916. Available at: https://pubmed.ncbi.nlm.nih.gov/16424443/ (Accessed: 11 September 2025).

54. Monahan, K., Storfer-Isser, A., Mehra, R., Shahar, E., Mittleman, M., Rottman, J., Punjabi, N., Sanders, M., Quan, S.F., Resnick, H. and Redline, S. (2009). 'The Association between Nocturnal Cardiac Arrhythmias and Sleep Disordered Breathing: The DREAM Study'. *Journal of Clinical Sleep Medicine*, 5(1), pp. 21-25. Available at: https://www.researchgate.net/publication/297730467_The_Association_between_Nocturnal_Cardiac_Arrhythmias_and_Sleep_Disordered_Breathing_The_DREAM_Study (Accessed: 11 September 2025).

55. Le Dolley, Y., Thambo, J.B., Fest, T., De Guillebon, M., Ploux, S., Reuter, S., Laborderie, J., Haïssaguerre, M., Clementy, J. and Bordachar, P. (2019). 'Incidence of sleep apnea and association with atrial fibrillation in an unselected pacemaker population: Results of the observational RESPIRE study'. *HeartRhythm*, 16(5), S1-S2. Available at: https://www.researchgate.net/publication/335633520_Incidence_of_sleep_apnea_and_association_with_atrial_fibrillation_in_an_unselected_pacemaker_population_Results_of_the_observational_RESPIRE_study (Accessed: 11 September 2025).

56. Monahan, K., Storfer-Isser, A., Mehra, R., Shahar, E., Mittleman, M., Rottman, J., Punjabi, N., Sanders, M., Quan, S.F., Resnick, H. and Redline, S. (2016). 'The Association between Nocturnal Cardiac Arrhythmias and Sleep-Disordered Breathing: The DREAM Study'. *Journal of Clinical Sleep Medicine*, 12(6), pp. 829-837. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC4877315/ (Accessed: 11 September 2025).

57. Garrigue, S., Pépin, J.L., Defaye, P., Murgatroyd, F., Poezevara, Y., Clémenty, J. and Lévy, P. (2007). 'High Prevalence of Sleep Apnea Syndrome in Patients With Long-Term Pacing The European Multicenter Polysomnographic Study'. *Circulation*, 115(13), pp. 1703-1709. Available at: https://www.researchgate.net/publication/6454534_High_Prevalence_of_Sleep_Apnea_Syn

drome_in_Patients_With_Long-Term_Pacing_The_European_Multicenter_Polysomnographic_Study (Accessed: 11 September 2025).

58. Koehler, U., Fus, E., Grimm, W. and Pomykaj, T. (2013). 'Severe OSA Leading to Long Pauses in 24-h Holter ECG Reversed with CPAP'. *Sleep and Breathing*, 17(1), pp. 19-21. Available at: https://pdfs.semanticscholar.org/9759/faefe909a19cc2f293cb73199901e7a32776.pdf (Accessed: 11 September 2025).

59. McNicholas, W.T. (2013). 'Sleep apnoea and the heart'. *European Respiratory Review*, 22(129), pp. 333-336. Available at: https://publications.ersnet.org/content/errev/22/129/333 (Accessed: 11 September 2025).