Sleep Medicine 89 (2022) 104–113

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

Prevalence, types and treatment of bradycardia in obstructive sleep apnea - A systematic review and meta-analysis☆

Yao Hao Teo [a, 1], Ruobing Han [a, 1], Shariel Leong [a], Yao Neng Teo [a], Nicholas L. Syn [a], Caitlin Fern Wee [a], Benjamin Kye Jyn Tan [a], Raymond CC. Wong [a, b], Ping Chai [a, b], Pipin Kojodjojo [a, b], William KF. Kong [a, b], Chi-Hang Lee [a, b], Ching-Hui Sia [a, b, *, 2], Tiong-Cheng Yeo [a, b, 2]

[a] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, 10 Medical Drive, Singapore 117597
[b] Department of Cardiology, National University Heart Centre Singapore, 1E Kent Ridge Road, NUHS Tower Block Level 9, Singapore 119228

ARTICLE INFO

Article history:
Received 10 August 2021
Received in revised form
30 November 2021
Accepted 1 December 2021
Available online 10 December 2021

Keywords:
Obstructive sleep apnea (OSA)
Bradyarrhythmia
Sinus bradycardia
Sinus arrest
Atrioventricular block
Continuous positive airway pressure (CPAP)

ABSTRACT

Background: The association of obstructive sleep apnea (OSA) with bradycardia is not well-characterized, which may confer significant morbidity and mortality if left untreated. We sought to clarify the prevalence of comorbid OSA and bradycardia, and the effect of continuous positive airway pressure (CPAP) therapy on bradycardia outcomes.

Methods: We systematically searched four electronic databases (PubMed, Embase, Cochrane Library, Scopus) for randomized or observational studies reporting the co-prevalence of sleep apnea and bradycardia or evaluated the use of CPAP on the incidence of bradycardias. We used random-effects models in all meta-analyses and evaluated heterogeneity using I^2.

Results: We included 34 articles from 7204 records, comprising 4852 patients. Among patients with OSA, the pooled prevalence of daytime and nocturnal bradycardia were 25% (95% CI: 18.6 to 32.7) and 69.8% (95% CI: 41.7 to 88.2) respectively. Among patients with bradycardia, the pooled prevalence of OSA was 56.8% (95% CI: 21.5 to 86.3). CPAP treatment, compared to those without, did not significantly reduce the risk of daytime (two randomized trials; RR: 0.50; 95% CI: 0.11 to 2.21) or nocturnal bradycardia (one randomized-controlled trial and one cohort study; RR: 0.76; 95% CI: 0.48 to 1.20).

Conclusions: This meta-analysis demonstrates a high comorbid disease burden between OSA and bradycardia. Future research should explore the treatment effect of CPAP on bradycardia incidence, as compared to placebo.

1. Introduction

OSA is a public health issue affecting approximately one-seventh of the world's adult population [1]. Globally, over 900 million adults aged 30–69 have OSA, out of which over 400 million people have moderate to severe disease [2]. OSA is characterized by recurrent narrowing of upper airway during sleep, leading to complete or partial cessation of air flow. This in turn causes increased negative intrathoracic pressure, sleep fragmentation, and intermittent hypoxia during sleep [3]. OSA is known to be associated with many serious and even fatal cardiovascular comorbidities, including hypertension, coronary artery disease, heart failure, stroke, and type 2 diabetes mellitus [4–8]. In 2015, the estimated cost burden of undiagnosed OSA among US adults was $149.6 billion, and the estimated cost of diagnosing and treating OSA in the US was $12.4 billion [1].

Bradycardias such as sinus arrest and high-degree atrioventricular blocks may confer high morbidity and mortality if left untreated [9]. Hence, the identification and treatment of reversible causes of bradycardia is highly sought after. There is emerging evidence that OSA is associated with cardiac

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author. Department of Cardiology, National University Heart Centre Singapore, 1E Kent Ridge Road, NUHS Tower Block Level 9, Singapore 119228.
E-mail address: ching_hui_sia@nuhs.edu.sg (C.-H. Sia).

[1] Both authors contributed equally to this manuscript.
[2] Both authors supervised this manuscript equally.

https://doi.org/10.1016/j.sleep.2021.12.003
1389-9457/

arrhythmias [10], especially tachyarrhythmias such as atrial fibrillation [10] and ventricular tachyarrhythmia [11]. However, the association between OSA and bradycardia is less well-characterized. While previous studies have reported on the prevalence of bradycardia in OSA patients, there are large differences in the proportions observed [12,13]. These studies often recruited smaller cohorts of fewer than 100 subjects, and differed in their definition of bradycardia and inclusion of the different types of bradyarrhythmias.

Continuous positive airway pressure (CPAP) is a well-established efficacious therapy for OSA patients [14]. However, limited evidence exists for its efficacy in improving cardiovascular outcomes. While there have been reports of the benefits of CPAP treatment on arrhythmias [15], heart failure [16], and hypertension [17], previous meta-analyses did not demonstrate any significant risk reduction in cardiovascular outcomes with CPAP treatment [18,19].

While OSA has been reported in patients with bradycardia, including sinus bradycardia and atrioventricular blocks [13,20,21], to the best of our knowledge, there is no comprehensive review on the coprevalence between OSA and bradycardic cardiac rhythms. Therefore, our study aims to comprehensively review firstly, the co-prevalence between OSA and bradycardia, such as severe sinus bradycardia and high-degree atrioventricular blocks, and secondly, whether the use of CPAP was associated with an improvement in bradycardia.

2. Methods

This meta-analysis was registered on PROSPERO (CRD42021 227953) and is reported in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [22]. The PRISMA checklist [22] is included in Supplemental Table 1.

2.1. Search Strategy

Literature search of four electronic databases (PubMed, Embase, Cochrane Library, Scopus) was performed on 21st December 2020 for articles published from date of inception till 21st December 2020 using the following free text search strategy (obstructive sleep apnea or sleep apnea OR sleep apnea syndrome OR sleep apnea hypopnea syndrome OR apnea OR OSA OR OSAs OR OSAHS OR nocturnal hypoxia OR nocturnal hypoxemia OR sleep disturbed breathing OR CPAP OR nCPAP OR continuous positive airway pressure) AND (bradycardia OR arrhythmia OR sinus bradycardia OR junctional bradycardia OR idioventricular bradycardia OR AVB or AV block or atrioventricular block). The term “sleep-disordered breathing” was not used in the search strategy as it is a heterogenous umbrella term that includes primary snoring, OSA, central sleep apnea and sleep-related hypoventilation syndromes [23,24].

2.2. Study Selection

Following the inclusion and exclusion criteria detailed in the PICOS table (Table 1), two authors independently selected potentially eligible studies using the data management software Rayyan QCRI [25]. The initial screening was based on title and abstract, while final inclusion was based on full texts where available. We included randomized controlled trials and observational studies reporting the co-prevalence of sleep apnea and bradycardia. We accepted the presence or severity of sleep apnea measured by the apnea-hypopnea index (AHI), respiratory disturbance index (RDI), clinical diagnosis according to the International Classification of Diseases (ICD) diagnostic codes, as well as the presence or severity of nocturnal hypoxemia measured by pulse oximetry or any other objective measurements or indices of oxygen saturation eg. sleep duration with arterial oxygen saturation <90% (T90%), oxygen desaturation index (ODI) etc. We accepted conference abstracts, academic dissertations, and other grey literature as per protocol if they fulfilled the above criteria. Additionally, we searched for studies that evaluated the use of continuous positive airway pressure (CPAP) therapy, the gold standard for treatment of OSA [14], on the incidence of bradyarrhythmias.

We considered all types of bradyarrhythmias, including overall bradycardia, severe bradycardia (<30/minute), sinus node disease such as sinus bradycardia or sinus arrest, and atrioventricular nodal disease (AV disease) such as junctional bradycardia, idioventricular bradycardia or AV block. The following study types were excluded: case reports, reviews, letters, and non-English publications.

2.3. Data Extraction

Two authors extracted the following data from each article into a standardized extraction spreadsheet template: first author, year published, study design, setting, country, sample size, percentage male, mean/median age, body mass index (BMI), intervention/exposure (where applicable), outcomes, covariates, statistical methods, and key findings.

2.4. Statistical Analysis

We found sufficient data in our systematic review to meta-analyze the pooled mean prevalence with 95% confidence intervals for OSA and bradycardia. We computed pooled prevalence or cumulative incidences using the one-step generalized linear mixed-effects model (GLMM) method using the metaprop_one routine in Stata (version 16.0, StataCorp), which has been shown to yield less biased estimates, smaller errors and greater coverage probabilities than traditional two-stage methods [26,27]. When the one-stage model failed to converge, an inverse variance-weighted random-effects meta-analysis using the Freeman Tukey double-arcsine transformation was used to pool proportions. All graphical representations of pooled proportions were reported in Supplemental Fig. 1. The risk ratios of CPAP treatment and placebo on bradycardia were quantitatively pooled and analyzed using Review Manager (RevMan) Version 5.4 [28], using general approaches laid out by the Cochrane Handbook [29]. We used random-effects models in all analyses to account for anticipated heterogeneity in the observational estimates [30], and assessed between-study heterogeneity using the I^2 statistic [31]. An I^2 of <30% indicates low heterogeneity between studies, I^2 of 30–60% indicates moderate heterogeneity, and I^2 of >60% to indicate substantial heterogeneity. There were insufficient studies (<10 per outcome) to assess publication bias via visual inspection of funnel plot asymmetry, Egger's bias or trim-and-fill as planned [32–34]. A two-sided P value of <0.05 was considered as statistically significant.

2.5. Quality of Evidence

The Newcastle–Ottawa Scale (NOS) was utilized for observational studies to evaluate the risk of bias at the study level (Supplemental Table 2) [35,36]. Two authors independently assessed studies as having a high (<5 stars), moderate (5–7 stars), or low risk of bias (≥8 stars) according to the NOS grading in past reviews [37,38]. Cochrane risk of bias tool [39] was utilized for randomized-controlled trials (Supplemental Table 2).

Table 1
PICOS, inclusion criteria and exclusion criteria applied to database search.

PICOS	Inclusion Criteria	Exclusion Criteria
Population	• Patients with obstructive sleep apnea, sleep apnea, sleep apnea syndrome, sleep apnea hypopnea syndrome, apnea, nocturnal hypoxia, nocturnal hypoxemia, or sleep disturbed breathing	
Intervention	• CPAP, nCPAP, or continuous positive airway pressure	
Comparison	• Non-optimal CPAP use, or non-CPAP use, placebo (SHAM CPAP)	
Outcome	• Bradycardia, sinus bradycardia OR sinus arrest OR junctional bradycardia OR idioventricular bradycardia OR AVB or AV block or atrioventricular block OR severe bradycardia	
Study design	• Articles in English or translated to English • Randomized controlled trials • Mixed methods research, Cohort studies, case–control studies • Cross-sectional studies • Grey Literature/conference abstracts/electronic and print information not controlled by commercial publishing, of original data • Databases: PubMed, Embase, Cochrane, SCOPUS	• Meta-analyses, systematic reviews, and descriptive papers • Case reports and series, ideas, editorials, and perspectives

3. Results

The study selection process is summarized in Fig. 1. Our systematic search retrieved 7204 results. A total of 1504 duplicates were removed. Title and abstract screening excluded a further 5550 articles. Full text screening excluded 116 articles. Thirty-four articles were included in the review [13,20,21,40–66].

3.1. Baseline characteristics

The 34 studies comprised a combined cohort of 4852 patients. All studies reported OSA. The participant characteristics of the included studies are shown in Table 2. Across the 34 cohorts, 17 were retrospective and 17 were prospective. 14 studies were conducted in North America, 12 studies in Europe, two studies in Oceania, and eight in Asia. Mean age of participants ranged from 44 to 67.9 years old, and majority of studies recruited predominantly male participants, with the percentage of male participants ranging from 50 to 87%. Follow-up duration ranged from one day to 1.3 years. The studies reported daytime bradyarrhythmia, nocturnal bradyarrhythmia, or both. Bradyarrhythmias included sinus bradycardia, atrioventricular blocks, interventricular block, and sinus arrest. 15 studies further discussed the effects of CPAP treatment on bradycardia. The mean compliance rate to CPAP ranged from 84 to 100% and the mean duration of CPAP follow-up ranged from 1 day to 54 months.

3.2. Bradycardia prevalence in patients with OSA

3.2.1. Daytime bradycardia prevalence in patients with OSA

The prevalence of daytime bradycardia in patients with OSA is presented in Table 3. In patients with OSA, the pooled prevalence of daytime bradycardia is 25% (95% CI: 18.6 to 32.7). Among sinus node disease, the pooled prevalence of sinus bradycardia and sinus arrest were 18.3% and 7.3%, respectively. Among atrioventricular nodal disease, the pooled proportions of overall atrioventricular nodal disease and second-degree atrioventricular block were 6.1% and 2.4%, respectively. The pooled prevalence of severe bradycardia was 1.6%. Only one study [20] reported the prevalence of first-degree atrioventricular block at 23.4%.

3.2.2. Nocturnal bradycardia prevalence in patients with OSA

The prevalence of nocturnal bradycardia in patients with OSA is presented in Table 3. In patients with OSA, the pooled prevalence of nocturnal bradycardia was 69.8% (95% CI: 41.7 to 88.2). Among sinus node disease, the pooled prevalence of sinus bradycardia and sinus arrest were 30.5% and 16.5%, respectively. Among atrioventricular nodal disease, the pooled prevalence of overall atrioventricular nodal disease, combined second-degree and third-degree atrioventricular block, second-degree atrioventricular block, and 3rddegree atrioventricular block, were 9.9%, 10.8%, 2.3%, and 6.9%, respectively. One study [53] reported the prevalence of first-degree atrioventricular block at 4.35%. One study [59] reported the prevalence of severe sinus bradycardia at 40%. One study [61] reported the prevalence of interventricular conduction block at 3.7%.

3.3. Odds of bradycardia in patients with OSA

3.3.1. Odds of sinus nodal bradyarrhythmia in patients with OSA

We calculated the odds ratio (OR) for incidence of different bradycardia in patients with OSA. The OR of daytime and nocturnal sinus nodal bradycardia in patients with OSA is presented in Fig. 2. Compared to non-OSA patients, patients with OSA were associated with higher odds (OR: 10.04; 95% CI: 1.44–70.16) of daytime sinus nodal bradycardia.

3.3.2. Odds of atrioventricular nodal bradyarrhythmia in patients with OSA

The OR of daytime and nocturnal atrioventricular nodal bradycardia in patients with OSA is presented in Fig. 3. There were no significant associations observed for OSA and daytime and nocturnal atrioventricular nodal bradycardia.

3.4. OSA prevalence in patients with bradycardia

The prevalence of OSA in patients with bradycardia is presented in Table 3. Among patients with bradycardia, the pooled prevalence of OSA was 56.8% (95% CI: 21.5 to 86.3). One study [67] reported the prevalence of OSA in sinus node disease and atrioventricular nodal disease at 48% and 43.1%, respectively.

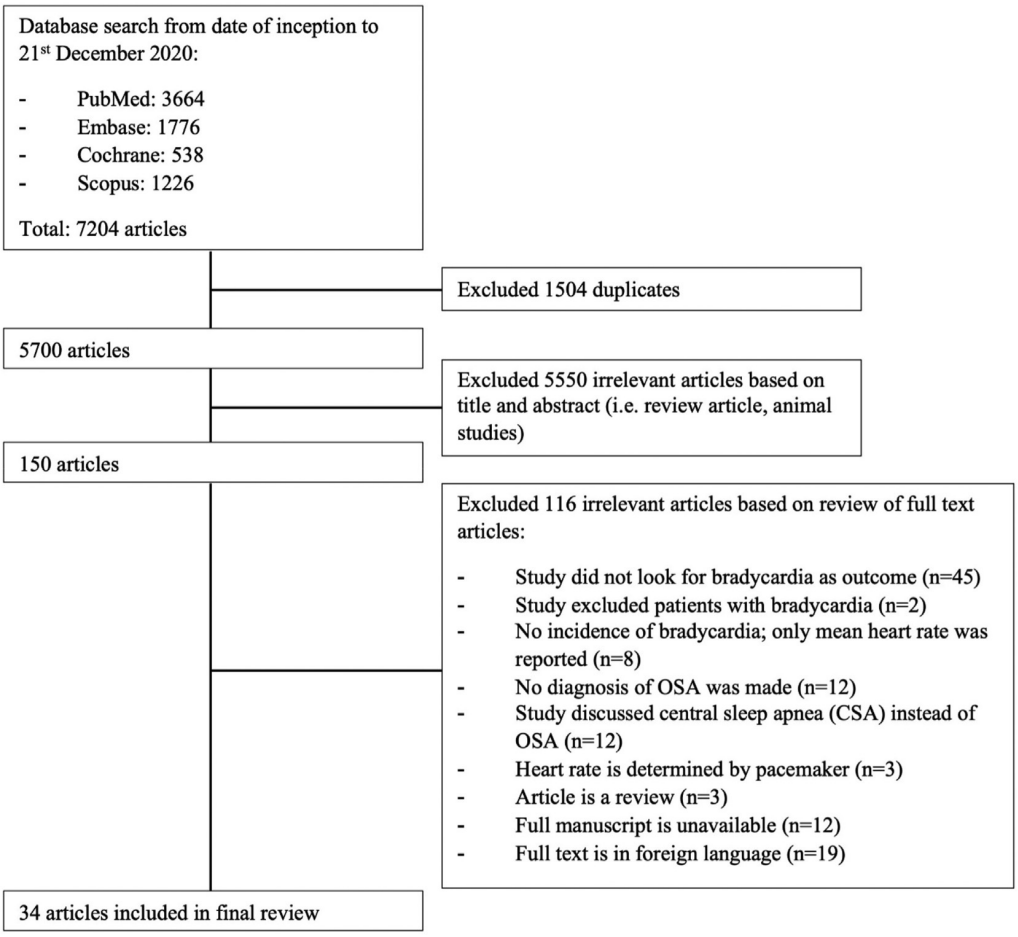

Fig. 1. PRISMA flowchart.

3.5. CPAP treatment

Of the six studies that evaluated the use of CPAP, only two studies compared CPAP to non-CPAP. In patients with OSA, comparing CPAP treatment to those without, there were no significant association between CPAP treatment and daytime bradycardia (two randomized-controlled trials; RR: 0.50; 95% CI: 0.11 to 2.21; Table 3) or nocturnal bradycardia (one randomized-controlled trial and one cohort study; RR: 0.76; 95% CI: 0.48 to 1.20; Table 3).

4. Discussion

In this meta-analysis of 34 studies with a combined cohort of 4852 patients, we demonstrated that the daytime and nocturnal prevalence of bradycardia in patients with OSA was 25% and 69.8%, respectively. Moreover, 56.8% of patients with bradycardia had OSA. This suggests a significant comorbidity between OSA and bradycardia. This finding is further supported by the higher odds of daytime sinus nodal bradycardia in patients with OSA. While there were no significant association observed between OSA and other bradycardia, we observed an increased signal towards higher odds of bradycardia in patients with OSA. We postulate that this was due to paucity of studies available and future prospective studies are required to clarify our findings. We also found that treatment of OSA with CPAP did not result in a statistically significant relative risk reduction in daytime and nocturnal bradycardia. This may be due to the limited number of studies and the small number of subjects recruited for those studies, and further research is needed to explore the association between CPAP treatment and bradycardia risk.

OSA is a condition that involves repeated upper airway collapse and oxygen desaturation during sleep [68]. It has been proposed that OSA causes bradycardia due to negative intrathoracic pressure from the stretch of thoracic cavity [69,70]; moreover, hypoxemia may also induce a vagally-mediated cardioprotective mechanism [71,72]. Furthermore, the cessation of breathing, together with hypoxemia seen in OSA, is necessary to cause bradycardia [73]. Lastly, it has been thought that hypoxemia causes the complete elimination of cyclic lung stretch, resulting in bradycardia [74]. In the first meta-analysis examining the co-prevalence of OSA and bradycardia, we demonstrated that

Table 2
Baseline Characteristics Table.

First Author, Year	DOI	Study Design	Sample Size	Country	Mean Age	% Male	Follow-Up Duration	Types of Bradycardias Reported	CPAP (Duration of CPAP per Night, Mean Follow-Up Duration of CPAP)	NOS
Abe, 2010	10.1007/s00380-009-1164-z	Prospective, cohort	1350	Japan	57.2	78.8	3.9 weeks	Nocturnal Sinus bradycardia (n = 66) 2nd-degree atrioventricular block (n = 13) 3rd-degree atrioventricular block (n = 1) Sinus pause (n = 57)	Yes (NR, 3.9 weeks)	5
Alonso-Fernández, 2005	10.1378/chest. 127.1.15	Retrospective, cross sectional	21	United States	54	90.5	NR	Daytime & Nocturnal Sinus bradycardia (n = NR) Sinus pause (n = NR)	No	7
Bayram, 2010	10.3906/sag-0910-355	Retrospective, cross sectional	63	Turkey	46.7 ± 10.4	79.4	NR	Daytime Sinus bradycardia (n = 2) Sinus arrest (n = 6) 2nd-degree atrioventricular block (n = 1) 3rd-degree atrioventricular block (n = 1)	No	8
Becker, 1993	(No DOI)	Prospective, cohort	10	Germany	43.4	90.0	NR	Nocturnal 2nd- & 3rd-degree atrioventricular block (n = 2) Sinus arrest (n = 8)	Yes (NR, NR)	3
Becker, 1995	10.1164/ajrccm.151.1.7812557	Prospective, cohort	239	Germany	50.7	94.1	NR	Daytime Sinus arrest (n = NR) Atrioventricular block (n = NR)	Yes (NR, 1 month)	4
Cheong, 1992	10.1159/000470327	Prospective, cohort	24	Canada	51 ± 2	87.5	1 day	Daytime Sinus pause (n = 2)	Yes (NR, 1 day)	4
Choudhary, 2019	10.1016/j.chest.2019.08.889	Retrospective, case control	110	United States	62	65.5	16 ± 4 months	Daytime Severe sinus bradycardia (n = 41) Sinus pause (n = 17) 2nd-degree atrioventricular block (n = 43) 3rd-degree atrioventricular block (n = 9)	Yes (NR, 16 ± 4 months)	6
Craig, 2009	10.1111/j.1365−2869.2008.00726.x	Prospective, randomized controlled trial	83	England	49.5	100	4 weeks	Daytime & Nocturnal Sinus bradycardia (n = 10) Sinus pause (n = 24)	Yes (4.6 h, 4 weeks)	6
Daccarett 2008	10.1016/j.amjcard.2007.11.068	Retrospective, case control	19	United States	64 ± 18	68.4	NR	Daytime Sinus pause Sinus bradycardia	No	6
Fietze 2000	10.1159/000029509	Retrospective, case control	192	Switzer-land	62.2 ± 12.2	52.1	NR	Daytime Sick sinus syndrome (n = 48) Atrioventricular block (n = 25) Atrial fibrillation with bradycardia (n = 11)	No	8
Flemons 1993	10.1164/ajrccm/148.3.618	Retrospective, case control	76	United States	48.5 ± 11.3	86.8	NR	Daytime 2nd-degree atrioventricular block (n = 1) Sinus arrest (n = 4)	No	6
Grimm 2000	10.1016/S0002-9149(00)01055-9	Prospective, cohort	29	United States	49	93.1	54 months	Daytime & Nocturnal Sinus bradycardia (n = 15) 3rd-degree atrioventricular block (n = 11) Sinus pause (n = 12)	Yes (NR, 54 months)	5
Harbison 2000	10.1378/chest.118.3.591	Prospective, cohort	45	United States	50	91.1	2−3 days	Daytime & Nocturnal 2nd-degree atrioventricular block (n = 1) Sinus pause (n = 7)	Yes (NR, 2−3 days)	5
Heneghan 2008	10.5664/JCSM. 27184	Retrospective, cross sectional	65	Ireland	42.2	−	NR	Nocturnal Sinus bradycardia (n = 61) Sinus pause (n = 3)	No	8
Jain 2020	10.1016/j.sleep.2020.05.034	Prospective, cohort	32	Nether-lands	44.11 ± 8.13	63.2	NR	Daytime Sinus bradycardia (n = 4)	No	5
Koehler, 1998		Prospective, cohort	16	Germany	49.6 ± 10.4	87.5	NR		Yes (NR, NR)	2

	10.1183/09031936.98.11020434							Nocturnal Sinus arrest (n = NR) Atrioventricular block (n = NR)		
Kwon, 2016	10.1007/s11325-016-1326-z	Retrospective, case control	471	United States	76.9	100	NR	Daytime Sinus bradycardia (n = 197) 1st-degree atrioventricular block (n = 110)	No	5
Men, 2011	10.1136/heartjnl-2011-300867.614	Prospective, cohort	446	China	–	–	NR	Daytime Sinus bradycardia (n = 86)	Yes (>6 h, NR)	6
Miller, 1982	10.1016/0002−9343(82)90716-1	Retrospective, cross sectional	23	United States	–	87.0	NR	Nocturnal Sinus bradycardia (n = 2) 1st-degree atrioventricular block (n = 1) 2nd-degree atrioventricular block (n = 1) Daytime Sinus pause (n = 2)	No	5
Olmetti, 2008	10.1016/j.sleep.2007.08.015	Retrospective, cross sectional	247	Nether-lands	54.3	–	NR	Nocturnal 2nd- and 3rd-degree atrioventricular block (n = 3) Sinus pause (n = 8)	No	7
Padeletti, 2010	10.1111/j.1540−8159.2010.02881.x	Prospective, cohort	11	United States	78.8 ± 8.0	72.7	487 ± 166 days	Daytime Sinus bradycardia (n = 5) 2nd- and 3rd-degree atrioventricular block (n = 4)	No	7
Patil, 2020	10.1016/j.chest.2020.05.482	Retrospective, cross sectional	100	India	–	–	NR	Nocturnal Sinus bradycardia (n = 40)	No	0
Poupard, 2012	10.1007/s11325-011-0558-1	Prospective, cohort	110	Germany	53	62.7	NR	Nocturnal Sinus bradycardia (n = 2) Sinus pause (n = 1)	Yes	3
Ryan, 2010	(No DOI)	Retrospective, cross sectional	165	United States	–	–	3 months	Daytime Sinus bradycardia (n = 2) Sinus pause (n = 1)	Yes (NR, 3 months)	2
Svanborg, 1990	10.1378/chest.98.6.1341	Retrospective, cross sectional	77	United States	49	89.6	NR	Nocturnal Sinus bradycardia (n = 39)	No	4
Szajerska Kurasiewicz, 2019	10.1093/eurheartj/ehz745.0641	Retrospective, case control	118	Poland	60	83.1	NR	Daytime Sinus bradycardia (n = 19) Atrioventricular block (n = 8) Sinus arrest (n = 7)	No	8
Tilkian, 1977	10.1016/0002−9343(77)90272-8	Retrospective, case control	15	United States	44	100	NR	Nocturnal Sinus bradycardia (n = 6) 2nd-degree atrioventricular block (n = 2) Sinus pause (n = 5)	No	6
Velasco, 2014	10.2459/JCM.0b013e3283630d07	Retrospective, cross sectional	190	United States	63	50.0	NR	Daytime 3rd-degree atrioventricular block (n = 16)	No	5
Wang, 2002	(No DOI)	Retrospective, cross sectional	35	China	–	–	NR	Daytime Sinus bradycardia (n = 12) 2nd-degree atrioventricular block (n = 6)	No	6
Wang, 2018	10.1097/MBP.0000000000000324	Prospective, cohort	214	China	48.56	84.1	2–3 days	Nocturnal Sinus arrest (n = 9) 1st- and 2nd-degree atrioventricular block (n = 16) Interventricular conduction block (n = 8)	Yes (NR, 2–3 days)	7
Wang, 2019	10.1007/s11596-019-1999-1	Prospective, cohort	64	China	53	59.4	3 months	Nocturnal Sinus bradycardia (n = 49) 2nd- to 3rd-degree atrioventricular block (n = 19) Sinus pause (n = 16)	Yes (NR, 3 months)	5

(*continued on next page*)

Table 2 (*continued*)

First Author, Year	DOI	Study Design	Sample Size	Country	Mean Age	% Male	Follow-Up Duration	Types of Bradycardias Reported	CPAP (Duration of CPAP per Night, Mean Follow-Up Duration of CPAP)	NOS
Wang, 2020	10.1016/j.amjoto.2020.102655	Prospective, randomized control trial	108	China	53	0.75	12 weeks	Nocturnal Sinus bradycardia (n = 83) 3rd-degree atrioventricular block (n = 57) Sinus pause (n = 32)	Yes (>4 h, 12 weeks)	6
Wu, 2016	10.1186/s12931-016-0333-8	Prospective, cohort	72	China	51	84.7	3 days	Nocturnal 3rd-degree atrioventricular block (n = 28) Sinus pause (n = 40)	Yes (>4 h on third day, 3 days)	6
Yilmaz, 2006	10.1016/j.ijporl.2006.03.005	Prospective, cohort	25	Turkey	66 ± 15 months	52.0	1 month	Daytime 2nd-degree atrioventricular block (n = 1)	No	6

Abbreviations: CPAP: continuous positive airway pressure; NOS: Newcastle–Ottawa Scale.

OSA is a common comorbidity in patients with bradycardia. Our findings support the current guideline recommendation to screen for OSA in patients with nocturnal bradyarrhythmias [75]. Likewise, it may be prudent to screen all patients diagnosed with OSA for bradyarrhythmia.

The prospective cohort study *(Efficacy of Continuous Positive Airway Pressure on Arrhythmias in Obstructive Sleep Apnea patients)* [40] on patients suspected of having sleep apnea syndrome and who underwent polysomnography in Japan, demonstrated a significant relationship between OSA and arrhythmias, as well as the therapeutic efficacy of CPAP treatment for the prevention of OSA-associated arrhythmias in subjects with OSA. . In our pair-wise meta-analysis of two studies each, we could not demonstrate an association between the treatment of OSA with CPAP and bradycardia. While there was a directional trend favoring CPAP treatment, the inclusion of Craig 2009 [45] resulted in insignificant associations for both daytime and nocturnal bradycardia. We postulate that this finding in our pair-wise meta-analysis might be ascribed to differences in the treatment duration (Craig 2009 [45]: 4 weeks; Wang 2019 [63] and Wang 2020 [62]: 3 months), heterogeneity between studies (CPAP and daytime bradycardia: $I^2 = 87\%$; CPAP and nocturnal bradycardia: $I^2 = 80\%$), as well as the paucity of studies available (two studies included in each pair-wise analysis). In view of the fact that CPAP treatment is cost-effective from a societal perspective, particularly in the earliest phases of OSA treatment [1,76,77], these findings point to the increased need in future research to examine if CPAP treatment, compared to placebo arm, improves the prognosis of bradycardia and hence reduces the need for implantation of permanent pacemakers in patients with a reversible cause of bradycardia such as OSA [75].

Besides CPAP, other strategies to treat bradyarrhythmias in OSA, such as the implantation of pacemaker, have also been suggested [78]. However, a review by Schweitzer [79] concluded that the role of cardiac pacing in OSA remains controversial. Further studies are needed to evaluate the utility of pacing and other in treating bradyarrhythmias in OSA.

4.1. Strengths and Limitations

To the best of our knowledge, this is the first study comprehensively reviewing the co-prevalence between OSA and bradycardia. Nevertheless, our study should be interpreted in due consideration of the limitations. Firstly, our meta-analysis did not find any existing study whose length of follow-up was beyond 1.3 years, hence further studies with longer follow-up periods may be required to further characterize the effect of CPAP treatment on bradycardia. Secondly, there was a paucity of studies limiting the analysis and identification of the pooled prevalence of certain individual subtypes of bradycardia in OSA patients, namely first-degree atrioventricular block, severe sinus bradycardia, and interventricular block. In patients with sinus node disease and atrioventricular nodal disease, although our meta-analysis does suggest possible coprevalence with OSA, this trend was reported by only one study, suggesting room for future studies in this area. Thirdly, there is a paucity of studies on the effects of CPAP on bradycardia. This may partly explain the insignificant association observed in the pairwise meta-analysis of CPAP treatment on bradycardia. Further studies are required to determine the role of CPAP in treating bradycardia in OSA patients. Fourth, the use of beta-blockers was reported in only seven studies [20,21,45,46,54,60,62], with the prevalence of OSA patients on beta-blockers ranging from 4% [54] to 72% [62], hence we are unable to comment if this may have contributed to a higher prevalence of bradycardia.

Table 3
Outcome Characteristics Table.

Outcomes	Pooled outcomes (95% CI)	Number of patients (number of included studies)
Daytime Bradyarrhythmia in Patients with OSA		
Daytime bradycardia in patients with OSA	Random pooled ES 25.00 (18.61–32.71)	148 (3 studies)
Daytime sinus bradycardia in patients with OSA	Random pooled ES 18.28 (5.31–47.16)	1284 (7 studies)
Daytime sinus arrest in patients with OSA	Random pooled ES 7.25 (2.72–17.94)	588 (9 studies)
Daytime atrioventricular nodal disease in patients with OSA	Random pooled ES 6.07 (2.53–13.87)	1077 (10 studies)
Daytime 2nd-degree atrioventricular block in patients with OSA	Random pooled ES 2.36 (0.58–9.10)	238 (6 studies)
Daytime severe bradycardia in patients with OSA	Random pooled ES 1.59 (0.01–65.35)	157 (3 studies)
Nocturnal Bradyarrhythmia in Patients with OSA		
Nocturnal bradycardia in patients with OSA	Random pooled ES 69.79 (41.73–88.18)	249 (3 studies)
Nocturnal sinus bradycardia in patients with OSA	Random pooled ES 30.52 (7.88–69.28)	1741 (7 studies)
Nocturnal sinus arrest in patients with OSA	Random pooled ES 16.46 (7.07–33.78)	2373 (14 studies)
Nocturnal atrioventricular nodal disease in patients with OSA	Random pooled ES 9.94 (3.96–22.82)	2177 (11 studies)
Nocturnal 2nd- & 3rd-degree atrioventricular block	Random pooled ES 10.76 (2.20–39.32)	429 (4 studies)
Nocturnal 2nd-degree atrioventricular block in patients with OSA	Random pooled ES 2.31 (0.69–7.48)	1433 (4 studies)
Nocturnal 3rd-degree atrioventricular block in patients with OSA	Random pooled ES 6.89 (0.27–66.77)	1451 (3 studies)
OSA in Patients with bradyarrhythmia		
OSA in patients with bradycardia	Random pooled ES 56.80 (21.53–86.30)	319 (3 studies)
Effect of CPAP Treatment on Bradyarrhythmia		
CPAP treatment on incidence of daytime bradycardia	RR 0.50 (0.11–2.21)	147 (2 studies)
CPAP treatment on incidence of nocturnal bradycardia	RR 0.76 (0.48–1.20)	147 (2 studies)

Abbreviations (in order of appearance): OSA: obstructive sleep apnea; CPAP: continuous positive airway pressure; CI: confidence interval.

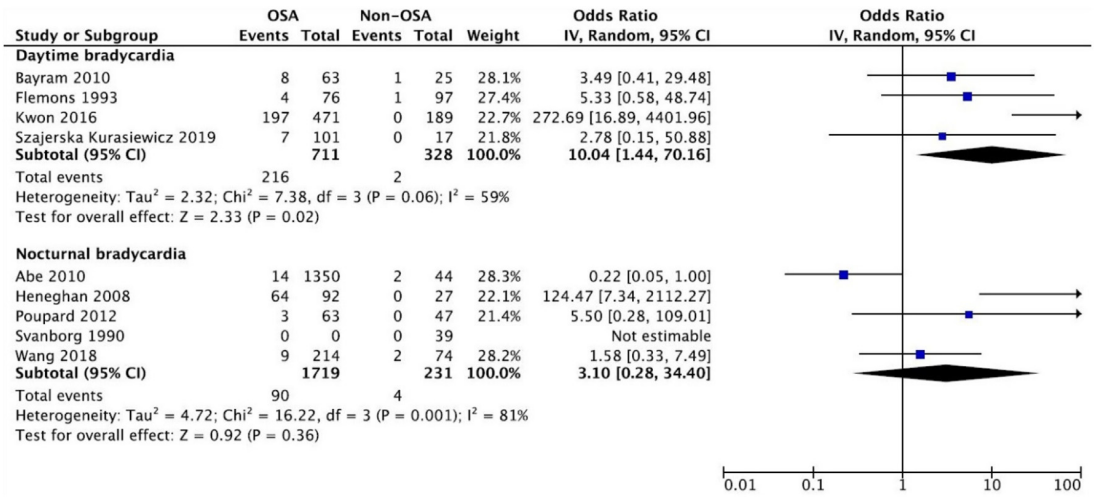

Fig. 2. Odds ratio of daytime and nocturnal sinus nodal bradycardia in OSA.

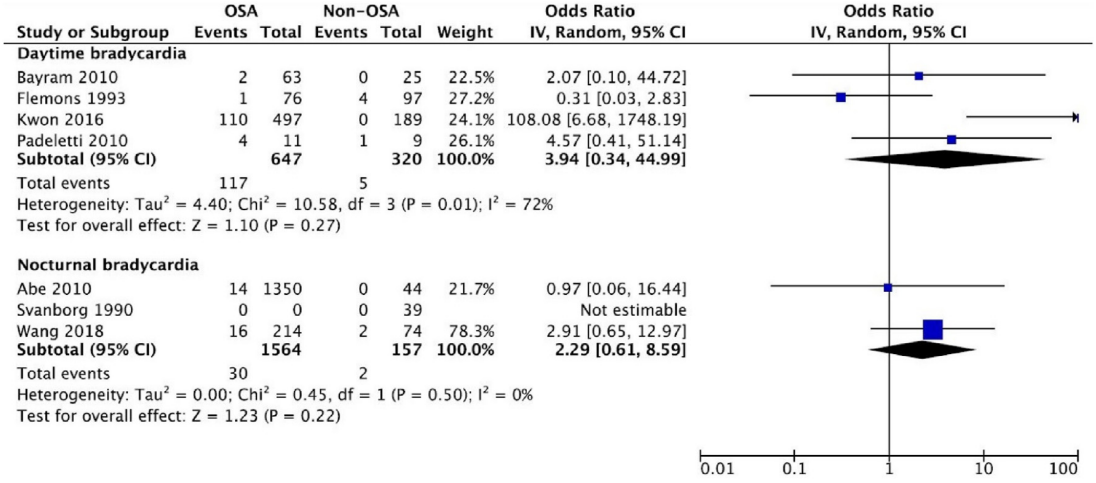

Fig. 3. Odds ratio of daytime and nocturnal atrioventricular nodal bradycardia in OSA.

5. Conclusion

In this meta-analysis, we demonstrated a high daytime and nocturnal prevalence of bradycardia in patients with OSA, at 25% and 69.8%, respectively. Moreover, 56.8% of patients with bradycardia had OSA, suggesting a high comorbidity between OSA and bradycardia. Our findings support the current guideline recommendation to screen for OSA in all patients with bradyarrhythmia. Likewise, it may be prudent to screen all patients diagnosed with OSA for bradyarrhythmias. These findings suggest that CPAP treatment for bradycardia in patients with OSA should be explored, and future research comparing CPAP treatment to placebo arm should be conducted to demonstrate the treatment effect of CPAP treatment for bradycardia.

Funding Sources

CS was supported by the National University of Singapore Yong Loo Lin School of Medicine's Junior Academic Faculty Scheme.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.12.003.

References

[1] Lyons MM, Bhatt NY, Pack AI, et al. Global burden of sleep-disordered breathing and its implications. Respirology 2020;25(7):690–702.
[2] Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019;7(8):687–98.
[3] Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22(5):667–89.
[4] Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 2000;283(14):1829–36.
[5] Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163(1):19–25.
[6] Redline S, Min NI, Shahar E, et al. Polysomnographic predictors of blood pressure and hypertension: is one index best? Sleep 2005;28(9):1122–30.
[7] Foster GD, Sanders MH, Millman R, et al. Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes Care 2009;32(6):1017–9.
[8] Sia CH, Hong Y, Tan LWL, et al. Awareness and knowledge of obstructive sleep apnea among the general population. Sleep Med 2017;36:10–7.
[9] Koehler U, Wetzig T, Peter JH, et al. Morbidity and mortality in sleep apnea and nocturnal bradyarrhythmia. Dtsch Med Wochenschr 1994;119(36):1187–93.
[10] Patel N, Donahue C, Shenoy A, et al. Obstructive sleep apnea and arrhythmia: a systemic review. Int J Cardiol 2017;228:967–70.
[11] Salama A, Abdullah A, Wahab A, et al. Is obstructive sleep apnea associated with ventricular tachycardia? A retrospective study from the National Inpatient Sample and a literature review on the pathogenesis of Obstructive Sleep Apnea. Clin Cardiol 2018;41(12):1543–7.
[12] Akar Bayram N, CiftcI B, Firat Guven S, et al. Prevalence of cardiac arrhythmia in obstructive sleep apnea syndrome. Turk J Med Sci 2010;40(6):843–50.
[13] Wang H, Zhang X, Yang Y, et al. Relationship between sleep apnea hypopnea syndrome and cardiovascular events in elderly Chinese snorers. Chin Med J 2002;115(12):1829–32.
[14] Spicuzza L, Caruso D, Di Maria G. Obstructive sleep apnoea syndrome and its management. Ther Adv Chronic Dis 2015;6(5):273–85.
[15] Rossi VA, Stradling JR, Kohler M. Effects of obstructive sleep apnoea on heart rhythm. Eur Respir J 2013;41(6):1439–51.
[16] Kato T, Suda S, Kasai T. Positive airway pressure therapy for heart failure. World J Cardiol 2014;6(11):1175–91.
[17] Martinez-Garcia MA, Capote F, Campos-Rodriguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013;310(22):2407–15.
[18] Labarca G, Dreyse J, Drake L, et al. Efficacy of continuous positive airway pressure (CPAP) in the prevention of cardiovascular events in patients with obstructive sleep apnea: systematic review and meta-analysis. Sleep Med Rev 2020;52:101312.
[19] Wang X, Zhang Y, Dong Z, et al. Effect of continuous positive airway pressure on long-term cardiovascular outcomes in patients with coronary artery disease and obstructive sleep apnea: a systematic review and meta-analysis. Respir Res 2018;19(1):61.
[20] Kwon Y, Picel K, Adabag S, et al. Sleep-disordered breathing and daytime cardiac conduction abnormalities on 12-lead electrocardiogram in community-dwelling older men. Sleep Breath 2016;20(4):1161–8.
[21] Padeletti M, Vignini S, Ricciardi G, et al. Sleep disordered breathing and arrhythmia burden in pacemaker recipients. Pacing Clin Electrophysiol 2010;33(12):1462–6.
[22] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[23] Carden KA, Chervin RD. Consistency and clarity in sleep medicine terminology. J Clin Sleep Med 2016;12(2):157–8.
[24] Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest 2014;146(5):1387–94.
[25] Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.
[26] Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Publ Health 2014;72(1):39.
[27] Lin L, Chu H. Meta-analysis of proportions using generalized linear mixed models. Epidemiology 2020;31(5).
[28] Version 5.4 Review manager (RevMan). The Cochrane Collaboration; 2020.
[29] Higgins JPTTJ, Chandler J, Cumpston M, et al. Cochrane handbook for systematic reviews of interventions. 2nd ed. The Cochrane Collaboration; 2019.
[30] DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clin Trials 1986;7(3):177–88.
[31] Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
[32] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50(4):1088–101.
[33] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
[34] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56(2):455–63.
[35] GA Wells BS, O'Connell D, Peterson J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 24 April 2019].
[36] Cochrane Collaboration. Section 13.5.2.3. Tools for assessing methodological quality or risk of bias in non-randomized studies. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions; 2011. Version 5.1.0. London.
[37] Kojima G, Avgerinou C, Iliffe S, et al. Adherence to mediterranean diet reduces incident frailty risk: systematic review and meta-analysis. J Am Geriatr Soc 2018;66(4):783–8.
[38] Saraiva MD, Suzuki GS, Lin SM, et al. Persistent pain is a risk factor for frailty: a systematic review and meta-analysis from prospective longitudinal studies. Age Ageing 2018;47(6):785–93.
[39] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[40] Abe H, Takahashi M, Yaegashi H, et al. Efficacy of continuous positive airway pressure on arrhythmias in obstructive sleep apnea patients. Heart Ves 2010;25(1):63–9.
[41] Akar Bayram NaÇ B, Firat Güven S, Bayram H, et al. Prevalence of cardiac arrhythmia in obstructive sleep apnea syndrome. Turk J Med Sci 2010;40(6):843–50.
[42] Alonso-Fernández A, García-Río F, Racionero MA, et al. Cardiac rhythm disturbances and ST-segment depression episodes in patients with obstructive sleep apnea-hypopnea syndrome and its mechanisms. Chest 2005;127(1):15–22.
[43] Becker H, Brandenburg U, Conradt R, et al. [Influence of nCPAP therapy on bradycardic arrhythmias in sleep apnea]. Pneumologie 1993;47(Suppl 4):706–10.
[44] Cheong TH, Sami M, Kimoff RJ, et al. Cardiac disturbances in patients with obstructive sleep apnea. Am J Noninvasive Cardiol 1992;6:47–54.
[45] Craig S, Pepperell JC, Kohler M, et al. Continuous positive airway pressure treatment for obstructive sleep apnoea reduces resting heart rate but does not affect dysrhythmias: a randomised controlled trial. J Sleep Res 2009;18(3):329–36.
[46] Daccarett M, Segerson NM, Hamdan AL, et al. Relation of daytime bradyarrhythmias with high risk features of sleep apnea. Am J Cardiol 2008;101(8):1147–50.
[47] Flemons WW, Remmers JE, Gillis AM. Sleep apnea and cardiac arrhythmias. Is there a relationship? Am Rev Respir Dis 1993;148(3):618–21.
[48] Grimm W, Koehler U, Fus E, et al. Outcome of patients with sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy. Am J Cardiol 2000;86(6):688–92. a689.

[49] Choudhary G, Lakshmanadoss U. Appropriate diagnosis and treatment of OSA: is it a new treatment for severe, asymptomatic bradyarrhythmias during sleep? Chest 2019;156(4):a961.
[50] Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. Chest 2000;118(3):591–5.
[51] Heneghan C, de Chazal P, Ryan S, et al. Electrocardiogram recording as a screening tool for sleep disordered breathing. J Clin Sleep Med 2008;4(3):223–8.
[52] Jain V, Kimbro S, Kowalik G, et al. Intranasal oxytocin increases respiratory rate and reduces obstructive event duration and oxygen desaturation in obstructive sleep apnea patients: a randomized double blinded placebo controlled study. Sleep Med 2020;74:242–7.
[53] Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. Prevalence and significance. Am J Med 1982;73(3):317–21.
[54] Olmetti F, La Rovere MT, Robbi E, et al. Nocturnal cardiac arrhythmia in patients with obstructive sleep apnea. Sleep Med 2008;9(5):475–80.
[55] Patil S. Sleep patterns in obese COPD patients with diabetes. Chest 2020;157(6):a429.
[56] Poupard L, Mathieu M, Goldman M, et al. Multi-modal ECG Holter system for sleep-disordered breathing screening: a validation study. Sleep Breath 2012;16(3):685–93.
[57] Ryan AR, Malow BA, Song Y, et al. Utility of overnight polysomnography in detecting cardiac arrhythmias. Sleep 2010;33(Supplement_1):a301.
[58] Szajerska-Kurasiewicz A, Loboda D, Simionescu K, et al. P3796Prediction of severe sleep apnea in patients with nocturnal bradycardia or conduction disorders. Eur Heart J 2019;40(Supplement_1).
[59] Tilkian AG, Guilleminault C, Schroeder JS, et al. Sleep-induced apnea syndrome. Prevalence of cardiac arrhythmias and their reversal after tracheostomy. Am J Med 1977;63(3):348–58.
[60] Velasco A, Hall C, Perez-Verdia A, et al. Association of high-risk scores for obstructive sleep apnea with symptomatic bradyarrhythmias. J Cardiovasc Med 2014;15(5):407–10.
[61] Wang X, Qiu J, Wang Y, et al. Beneficial response of blood pressure to short-term continuous positive airway pressure in Chinese patients with obstructive sleep apnea-hypopnea syndrome. Blood Pres Monit 2018;23(4):175–84.
[62] Wang X, Yue Z, Liu Z, et al. Continuous positive airway pressure effectively ameliorates arrhythmias in patients with obstructive sleep apnea-hypopnea via counteracting the inflammation. Am J Otolaryngol 2020;41(6):102655.
[63] Wang XT, Zhao G, Tu L, et al. Continuous positive airway pressure effectively alleviates arrhythmias in patients with obstructive sleep apnea: possible relationship with counteracting oxidative stress. Curr Med Sci 2019;39(1):52–8.
[64] Wu X, Liu Z, Chang SC, et al. Screening and managing obstructive sleep apnoea in nocturnal heart block patients: an observational study. Respir Res 2016;17:16.
[65] Xiaoqian M. Heart rhythm disorder in patients with obstructive sleep apnoea syndrome. Heart 2011;97(Suppl 3):A209.
[66] Yilmaz F, Gunduz H, Karaaslan K, et al. Holter analyses in children with adenotonsillar hypertrophy. Int J Pediatr Otorhinolaryngol 2006;70(8):1443–7.
[67] Fietze I, Röttig J, Quispe-Bravo S, et al. Sleep apnea syndrome in patients with cardiac pacemaker. Respiration 2000;67(3):268–71.
[68] Dempsey JA, Veasey SC, Morgan BJ, et al. Pathophysiology of sleep apnea. Physiol Rev 2010;90(1):47–112.
[69] Camen G, Clarenbach CF, Stowhas AC, et al. The effects of simulated obstructive apnea and hypopnea on arrhythmic potential in healthy subjects. Eur J Appl Physiol 2013;113(2):489–96.
[70] May AM, Van Wagoner DR, Mehra R. OSA and cardiac arrhythmogenesis: mechanistic insights. Chest 2017;151(1):225–41.
[71] Koehler U, Becker HF, Grimm W, et al. Relations among hypoxemia, sleep stage, and bradyarrhythmia during obstructive sleep apnea. Am Heart J 2000;139(1 Pt 1):142–8.
[72] Grimm W, Hoffmann J, Menz V, et al. Electrophysiologic evaluation of sinus node function and atrioventricular conduction in patients with prolonged ventricular asystole during obstructive sleep apnea. Am J Cardiol 1996;77(15):1310–4.
[73] Zwillich C, Devlin T, White D, et al. Bradycardia during sleep apnea. Characteristics and mechanism. J Clin Invest 1982;69(6):1286–92.
[74] Kato H, Menon AS, Slutsky AS. Mechanisms mediating the heart rate response to hypoxemia. Circulation 1988;77(2):407–14.
[75] Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines, and the heart rhythm society. J Am Coll Cardiol 2019;74(7):932–87.
[76] Tan MC, Ayas NT, Mulgrew A, et al. Cost-effectiveness of continuous positive airway pressure therapy in patients with obstructive sleep apnea-hypopnea in British Columbia. Cancer Res J 2008;15(3):159–65.
[77] Ayas NT, FitzGerald JM, Fleetham JA, et al. Cost-effectiveness of continuous positive airway pressure therapy for moderate to severe obstructive sleep apnea/hypopnea. Arch Intern Med 2006;166(9):977–84.
[78] Garrigue S, Bordier P, Jais P, et al. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002;346(6):404–12.
[79] Schweitzer P. Cardiac arrhythmias in obstructive sleep apnea. Vnitr Lek 2008;54(10):1006–9.