Effects of continuous positive airway pressure treatment in obstructive sleep apnea patients with atrial fibrillation

A meta-analysis

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Abstract

Background: Obstructive sleep apnea (OSA) is correlated with atrial fibrillation (AF). Over the past decade, there has been an increasing interest in the relationship between OSA with continuous positive airway pressure (CPAP) and progression or recurrence of AF.

Methods: This investigation was an analysis of studies searched in the Cochrane Library, PubMed, EMBASE, EBSCO, OVID, and Web of Science databases from inception to July 2020 to evaluate the recurrence or progression of AF in CPAP users, CPAP nonusers, and patients without OSA.

Results: Nine studies with 14,812 patients were recruited. CPAP therapy reduced the risk of AF recurrence or progression by 63% in a random-effects model (24.8% vs 40.5%, risk ratio [RR] = 0.70, 95% confidence interval [CI] = 0.57–0.85, P = .035). Compared with non-OSA patients, AF recurrence or progression was much higher in CPAP nonusers (40.6% vs 21.1%, RR = 1.70, 95% CI = 1.19–2.43, P = .000). However, AF recurrence or progression in the CPAP group was similar to that in the non-OSA group (24.0% vs 21.1%, RR = 1.13, 95% CI = 0.87–1.47, P = .001). Begg correlation test and Egger regression test revealed no publication bias in this analysis.

Conclusions: OSA is a salient factor in the progression or recurrence of AF. CPAP therapy for OSA may contribute to reduction of AF in patients for whom radiofrequency ablation or direct current cardioversion is not performed.

Trial Registration: The protocol for this meta-analysis was registered on PROSPERO with a registration No. CRD42019135229.

Abbreviations: AF = atrial fibrillation, CPAP = continuous positive airway pressure, CVD = cardiovascular disease, HIF-1α = hypoxia-inducible factor-1α, NF-kB = nuclear factor-kB, OSA = obstructive sleep apnea, ReML = restricted estimation maximum likelihood, RFA = radiofrequency ablation.

Keywords: atrial fibrillation, continuous positive airway pressure, meta-analysis, obstructive sleep apnea
1. Introduction
Atrial fibrillation (AF) is a highly prevalent arrhythmia that may induce severe cardiovascular outcomes.\textsuperscript{[1–3]} Epidemiological studies have showed that obstructive sleep apnea (OSA) is associated with an increased incidence and progression of coronary heart disease,\textsuperscript{[4]} heart failure,\textsuperscript{[5]} stroke,\textsuperscript{[6]} and AF.\textsuperscript{[7]} Recent studies strongly demonstrate that OSA could be an independent factor associated with AF.\textsuperscript{[8−9]} The most common pathophysiological mechanisms between OSA and AF have been explored, such as hypoxia due to apnea, intrathoracic pressure changes, sympathetic nerve maladjustment, atrial remodeling, oxidative stress, systematic inflammation, vascular dysfunction, and neurohumoral activation.\textsuperscript{[10–12]} Compared with patients without OSA, those with OSA are highly at high risk of developing AF and vice versa.\textsuperscript{[13]} Currently, antiarrhythmic drugs and catheter ablation are primary treatments feasible for maintaining the sinus rhythm in patients with AF. However, other means to reverse AF to sinus rhythm are not generally acknowledged. Continuous positive airway pressure (CPAP) therapy has become the principal treatment for OSA since 1981.\textsuperscript{[14]} However, it remains disputable whether CPAP should be preferred for treatment of AF\textsuperscript{[15,16]} This is largely because CPAP reverses atrial remodeling in patients with AF. Furthermore, platelet–lymphocyte ratio was considered as an independent indicator of cardiovascular disease (CVD) in OSA syndrome. CPAP treatment may impact platelet parameters and phenotype.\textsuperscript{[17]} Nonetheless, the studies reporting such findings were usually single-center experiences with a small patient sample and divergent outcomes. A meta-analysis investigating the association between CPAP therapy for AF and OSA should therefore be conducted.

2. Methods
Relevant articles published in the Cochrane Library, PubMed, EMBASE, EBSCO, OVID, and Web of Science databases from inception to July 2020 were searched. Key words and related medical subject headings were searched for obstructive sleep apnea, atrial fibrillation, and continuous positive airway pressure. We also retrieved entry terms such as sleep apnea hypopnea syndrome, upper airway resistance sleep apnea syndrome, CPAP, airway pressure release ventilation, and airway pressure release ventilation mode. There was no language or other restrictions. Reference lists of reviews and relevant articles were also manually searched. In addition, we tried to email the researchers for potential original data. Detailed search strategy was shown in (Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A22). Since all data were obtained from published articles, ethical approval was not necessary.

The following studies were included: randomized controlled trials (RCT), retrospective or prospective cohort studies, or case-control studies; studies comparing CPAP users with nonusers regarding OSA with AF; trials enrolling human participants aged >18 years diagnosed with OSA based on polysomnography or other criteria; and articles with data on OSA.

The following studies were excluded: trials that focused only on central sleep apnea, trials that did not report arrhythmia measures before and after CPAP usage, and data from unpublished studies available as abstracts. Recurrence or progression of AF was considered as the outcome measure. The outcome was not restricted to any specific follow-up period.

2.1. Data abstraction and quality assessment
Structured data obtained from each study included the title, name of the first author, publication year, country where the research was conducted, demographic, and characteristic data of participants, exposure measurement, methods used to identify AF, OSA definition, and CPAP application. Progression of AF type was defined as paroxysmal AF at baseline (or “first detected/new onset” AF becoming paroxysmal AF at the subsequent follow-up) becoming persistent or permanent at the last follow-up or persistent AF at baseline (or “first detected/new onset” AF becoming persistent AF at next available follow-up) becoming permanent at the last follow-up.\textsuperscript{[18]} The Newcastle–Ottawa scale was used to determine the quality of each study. Two investigators extracted data and appraised the study quality. Inconsistencies in any article retrieved were resolved through discussion with a senior investigator.

2.2. Statistical analysis
All statistical analyses were performed using Stata version 12.0 (Stata Corporation, College Station, TX). Heterogeneity among studies was assessed using Cochran $Q$ test and expressed with the $I^2$ value. A $P$ value of the Q test of $<.10$ was considered statistically significant. A random-effect model was employed according to the DerSimonian–Laird method.\textsuperscript{[19]} Publication bias was appraised using Begg correlation and Egger regression tests.\textsuperscript{[20]} Meta-regression was performed to investigate the effect of various characteristics. Restricted estimation maximum likelihood (ReML) was conducted to evaluate the slope significance. Subgroup and sensitivity analyses were performed to adjust effect values.

The protocol for this meta-analysis was registered on PROSPERO with a registration No. CRD42019135229.

3. Results
3.1. Study samples
A total of 1225 citations were identified after merging the duplicates; of these, 1142 were excluded. Therefore, 9 studies with 14,812 participants\textsuperscript{[15,16,18,21–26]} that examined the correlation between CPAP treatment for OSA and the recurrence or progression of AF were included in the final analysis (Fig. 1). The majority of studies in this analysis involved radiofrequency ablation (RFA) and AF recurrence. However, one study applied medical management instead of CPAP usage as a rhythm-control strategy\textsuperscript{[18]} and whereas 2 selected direct current cardioversion of AF.\textsuperscript{[23,27]} The study characteristics are presented in Table 1.

3.2. Study quality
All of the included studies were cohort studies: 5 prospective,\textsuperscript{[16,18,21,23,24]} 3 retrospective, and 1 RCT.\textsuperscript{[15,22,23,27]} Sample sizes were large in all but 2 studies (Holmqvist et al and Patel et al). All included studies were grade high quality by the Newcastle–Ottawa scale (Table 2). These 9 studies were involved in the analysis (Table 3).

3.3. Heterogeneity test
A significant heterogeneity was observed ($\tau^2=0.0465$, $P=.024$, $I^2=56.6\%$, risk ratio $[RR]=0.69$, 95% confidence interval
A sensitivity analysis was conducted and showed that the study by Farrehi et al exerted the greatest heterogeneity to this meta-analysis (Fig. 3). This study was omitted, resulting in a decreased heterogeneity (Tau = 0.0131, \( P = .220 \), \( I^2 = 27.3\% \), RR = 0.64, 95% CI = 0.54–0.76) (Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A18). The study by Farrehi et al was excluded because the population size of the CPAP group was smaller than that of the non-CPAP group, and the non-CPAP group included patients treated with 1 to 4 hours of CPAP per night. In addition, OSA was defined using the STOP-BANG questionnaire, which might not be accurate.

3.4. Publication bias

Nine studies were included to test the publication bias using the linear regression method and funnel plot (Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A19). Using Stata version 12.0, Egger bias yielded \( P = .884 \), and Begg test yielded \( P = .466 \), indicating no publication bias in this analysis.

3.5. Meta-regression

The meta-regression analysis based on the various characteristics such as study design, race, follow up, multiple factors, and disease condition besides radiofrequency mode did not impact the RR of AF recurrence or progression for the CPAP versus the non-CPAP group (Table 4).

3.6. Heterogeneity test in subgroup analysis

In the subgroup analysis, 7 studies were used to compare the AF recurrence in the CPAP, non-CPAP, and non-OSA groups. The heterogeneity significantly decreased to zero (Tau \( P = .99 \), \( I^2 = 0\% \)) from \( P = .000 \), \( I^2 = 91.9\% \), RR = 1.79, 95% CI = 1.19–2.43 between non-CPAP and non-OSA groups, after a subgroup analysis on radiofrequency mode (Fig. 4). The result of the
heterogeneity test between the CPAP and non-OSA groups was significantly reduced to zero from Tau² = 0.0752, P = .001, and I² = 72.3% (Fig. 5; Fig. S3, Supplemental Digital Content, http://links.lww.com/MD2/A20), with a subgroup analysis on radiofrequency mode or AF stage. Given the wide variety of study designs, the random-effect model was therefore adopted in both comparisons.

### 3.7. Subgroup statistical analysis

Overall, 1176 patients who sustained CPAP treatment, 987 treated with a non-CPAP regimen and 8887 without OSA. A random-effect model was administered to calculate the RR values of the two groups and to draw forest plots and demonstrated that the AF recurrence in the CPAP group was lower than that in the non-CPAP group (24.8% vs 40.5%, RR = 0.50, 95% CI = 0.37–0.68), but was significantly higher in the non-CPAP group than that in the non-OSA group (40.5% vs 21.1%, RR = 1.87). Therefore, no publication bias was observed in these subgroups.

### 3.8. Publication bias in subgroups

In the analysis of publication bias between the non-OSA and non-CPAP groups, Egger bias yielded P = .580 and Begg test yielded P = .548. In the analysis of publication bias between the non-OSA and CPAP groups, Egger bias yielded of P = .964 and Begg test yielded of P = .764. Therefore, no publication bias was observed in these subgroups.

### 4. Discussion

Our meta-analysis showed that AF recurrence in the CPAP group was lower than that in the non-CPAP group. Publication bias tests showed a reliable reduction in AF recurrence in patients with OSA and AF who received CPAP treatment. Similarly, the results revealed that AF recurrence in the non-CPAP group was significantly higher than that in the non-OSA group, indicating that patients with OSA who do not receive CPAP treatment have a higher possibility of having AF recurrence or progression than without OSA patients among all patients with AF. Conversely, AF recurrence was similar between the CPAP and non-OSA groups, with no significant difference between the 2 groups after combining the effect. The results of analysis of AF recurrence were similar between patients with OSA treated with CPAP as a regimen and patients without OSA. The findings show that patients with OSA have a 1.9-fold increased risk of AF recurrence compared with those without OSA. CPAP treatment for OSA is associated with a 0.6-fold reduction of AF recurrence or progression.

Emerging research highlights the complex interrelationships between sleep-disordered breathing and CVD, providing opportunities, and challenges for clinical research. A previous meta-analysis focused on the association between CPAP treatment for OSA and recurrent AF after RFA. CPAP treatment for OSA has been considered potentially beneficial for patients with AF even if RFA or direct current cardioversion is not performed. A majority of studies have evaluated AF recurrence after RFA. Patients with AF have an increased risk of OSA and those with OSA have an increased risk of AF.
Table 2
Quality assessment.

| First author | Fisher et al, 2015[21] | Fein et al, 2013[15] | Holmqvist et al, 2015[18] | Jongnarangsin et al, 2008[22] | Kanagala et al, 2003[23] | Naruse et al, 2013[24] | Nellai et al, 2010[16] | Patel et al, 2010[25] | Caples et al, 2018[27] |
|--------------|------------------------|---------------------|--------------------------|-----------------------------|-------------------------|------------------------|------------------------|------------------------|------------------------|
| Study | Cohort | Cohort | Cohort | Cohort | Cohort | Cohort | Cohort | Cohort | RCT |
| Country | USA | USA | USA | USA | USA | Japan | USA | USA | USA |
| Total no. | 247 | 92 | 10132 | 324 | 118 | 153 | 720 | 3000 | 34 |
| Radiofrequency | MD | MD | MD | MD | MD | MD | MD | MD | MD |
| mode of AF | PI | PI | PI | PI | PI | PI | PI | PI | PI |
| RCT | MD | MD | MD | MD | MD | MD | MD | MD | MD |

Table 3
Data analysis.

| Researcher | Year | Total | OSA | CPAP | non-CPAP | CPAP AF recurrence | Non-CPAP AF recurrence | Non-OSA | Non-OSA AF recurrence |
|------------|------|-------|-----|------|----------|---------------------|------------------------|---------|-----------------------|
| Fisher et al[21] | 2015 | 247 | 94 | 32 | 62 | 17 | 27 | 153 | — |
| Fein et al[15] | 2013 | 84 | 62 | 32 | 30 | 9 | 19 | 30 | 10 |
| Holmqvist et al[18] | 2015 | 10,132 | 1841 | 602 | 411 | 94 | 75 | 5349 | 984 |
| Jongnarangsin et al[22] | 2008 | 324 | 32 | 18 | 14 | 9 | 10 | 292 | 108 |
| Kanagala et al[23] | 2003 | 118 | 39 | 12 | 27 | 5 | 22 | 79 | 42 |
| Naruse et al[24] | 2013 | 153 | 116 | 82 | 34 | 25 | 18 | 37 | 8 |
| Nellai et al[16] | 2013 | 720 | 142 | 71 | 71 | 25 | 48 | 578 | 172 |
| Patel et al[25] | 2010 | 3000 | 640 | 315 | 325 | 105 | 178 | 2360 | 519 |
| Caples et al[27] | 2018 | 34 | 25 | 12 | 13 | 3 | 3 | 9 | — |

AHI = apnea-hypopnea index, CFAE = complex fractionated Atrial electrogram, PI = pulmonary venous isolation, RCT = randomized controlled trial, RFA = radiofrequency ablation.
Some studies have identified possible pathophysiological mechanisms to explain the relationship between OSA and AF over the years. Oxidative stress seems to be one of the main causes of endothelial injury in OSA patients. Hypoxia may cause endothelial cell damage in patients with OSA. CPAP treatment could improve the clinical characteristics of patients, reduce the serum levels of nuclear factor-κB (NF-κB), hypoxia-inducible factor-1α (HIF-1α),[33] NF-κB is an essential initiator of

**Figure 2.** Comparison of AF recurrence or progression in patients using a Forest plot. A pooled estimate of risk ratio (diamonds) and 95% confidence intervals (width of diamonds) summarizes the effect size using the random-effects model. 1 indicates no radiofrequency ablation, 2 indicates pulmonary venous isolation, and 3 indicates pulmonary venous isolation and complex fractionated atrial electrogram. CI = confidence interval, RR = risk ratio.

![Figure 2](image)

**Figure 3.** Sensitivity analysis for the meta-analysis.

| Study               | RR (95% CI)         | Weight |
|---------------------|---------------------|--------|
| R. Kanaga (2003)    | 0.89 (0.43, 1.66)   | 5.94   |
| K. Jongnarangsin (2008) | 0.70 (0.40, 1.24)   | 8.58   |
| D. Patel (2010)     | 0.61 (0.51, 0.73)   | 20.96  |
| A.S. Fein (2013)    | 0.44 (0.24, 0.82)   | 7.67   |
| Y. Naruse (2013)    | 0.56 (0.37, 0.91)   | 11.24  |
| T.G. Neilan (2013)  | 0.52 (0.37, 0.74)   | 14.40  |
| P.M. Farrehi (2015) | 1.22 (0.79, 1.88)   | 11.91  |
| F. Holmqvist (2015) | 0.86 (0.65, 1.13)   | 17.31  |
| S.M. Capies (2018)  | 1.08 (0.27, 4.37)   | 1.99   |
| Overall (I² = 51.7%, p = 0.035) | 0.70 (0.57, 0.85) | 100.00 |

NOTE: Weights are from random effects analysis.

![Figure 3](image)
inflammation and HIF-1α was the main factor to maintain the homeostasis of oxygen metabolism. Both can regulate gene transcription and posttranslational protein modification. \cite{34,35}

Intermittent hypoxia induced by repeated interruption of ventilation in rats can cause connexin disorders and atrial conduction abnormalities associated with atrial fibrosis. \cite{36} The incidence of spontaneous atrial premature beats was shown to be significantly shortened due to obstructive respiratory events, representing an effective trigger factor for spontaneous AF in both OSA human and pig models. \cite{37,38} Similar arrhythmogenic electrophysiological changes were noted in rat models of obesity and OSA. \cite{39} Furthermore, repeated obstructive respiratory

| Analysis    | N  | Reference          | Random-effects model | Fixed-effects model | Heterogeneity |
|-------------|----|--------------------|----------------------|---------------------|---------------|
|             |    |                    | RR (95%)             | P                   | RR (95%)      | P             |               |
| Study design| 9  | 15–16,18,21–26     | 0.52 (.35–0.79)      |                     | 0.54 (.45–0.66)| 64.9%         | 0.004         |
| Retrospective| 3  | 15,22,25           | 0.39 (.29–0.53)      |                     | 0.39 (.29–0.53)| 0.0%          | 0.574         |
| Prospective | 5  | 16,18,21,23,24     | 0.62 (.34–1.12)      |                     | 0.69 (.53–0.89)| 70.6%         | 0.009         |
| RCT         | 1  | 26                 | 1.11 (.18–6.97)      | 1.11 (.18–6.97)     |               |               |
| Stage       | 9  |                    |                      |                     |               |               |
| Recurrence  | 8  | 16,18,21–26        | 0.47 (.31–1.15)      | 0.43 (.34–.55)      |               |               |
| Progression | 1  | 18                 | 0.83 (.59–1.16)      | 0.85 (.59–1.16)     |               |               |
| Therapy     | 9  |                    |                      |                     |               |               |
| No          | 3  | 18,23,26           | 0.84 (.61–1.15)      | 0.84 (.61–1.15)     |               |               |
| PVI         | 2  | 15,21              | 0.50 (.10–3.71)      | 0.71 (.36–1.38)     |               |               |
| PVI + CFAE  | 4  | 16,22,24,25        | 0.38 (.29–.50)       | 0.38 (.29–.50)      |               |               |

Figure 4. Comparison between CPAP group and non-CPAP group. CPAP = continuous positive airway pressure.
events may result in mechanical atrial dilatation, atrial wall expansion, intermittent hypoxemia, and hypercapnia, sympathetic nerve activation, and subsequent hemodynamic fluctuations during and after apnea. Interestingly, serum HIF-1α levels might have significant diagnostic and even prognostic value in both OSA and CVD including AF. These factors also cause the causes of structural remodeling and myocardial injury. Atrial dilation might shorten the atrial instability, slow down conduction, and increase the number of interatrial conduction blockades in isolated Langendorf perfused rabbit hearts. Negative fluctuation in intrathoracic pressure during upper respiratory inhalation in OSA induces changes in left atrial extension and transmural pressure gradients, particularly in the thin-walled atrium, through pressure, volumetric load, and sympathetic tone changes. Chronic complications such as obesity and hypertension may play a key role in the progression of structural atrial matrix remodeling. Atrial electrical and structural remodeling are crucial factors in the AF pathogenesis.

CPAP is currently the best therapeutic treatment for moderate-to-severe OSA. Systolic and diastolic abnormalities in patients with OSA may be reversed as early as 3 months after initiating of CPAP therapy, which increasingly ameliorates cardiovascular remodeling for >1 year. CPAP therapy may promote more homogeneous atrial conduction in patients with OSA, which may mitigate the long-term risk of atrial arrhythmias. Neilan et al demonstrated that CPAP treatment is associated with lower blood pressure, LV mass, and LA size in patients with paroxysmal rather than persistent AF. Fein et al's study revealed no significant difference in the frequency of repeat ablations among CPAP users, CPAP nonusers, and patients without OSA. CPAP could ameliorate endothelial dysfunction and enhance the release of nitric oxide, an influential vasodilator in atherosclerosis and CVD development. Additionally, CPAP could mitigate the systemic inflammation and oxidative stress, another potential mechanism of CVD. A larger LA size is also associated with chronic AF progression, one of the predictors of surgical failure. All these factors may constitute the mechanisms of how CPAP treatment reduces recurrent AF exposure after catheter ablation.

According to the current data, CPAP therapy may be associated with a reduced recurrence or progression in patients with AF without RFA. These results suggest that CPAP therapy...
reverses the electrical and/or structural remodelling associated with OSA, thereby decreasing the incidence of AF recurrence. Future studies investigating the effects of CPAP on atrial and ventricular remodeling in patients with AF should consider the clinical significance of these findings. CPAP therapy can provide homogeneous conduction in the atrium and ventricle, which might reduce the risk of atrial and ventricular arrhythmias in the long-term. To date, no study has compared the status of patients with AF before and after RFA who have undergone CPAP therapy and further research in this field is needed to confirm CPAP, OSA, AF, and RFA in future randomized controlled trials.

4.1. Limitations
The strength of this study is that we comprehensively searched multiple databases including the Cochrane Library, PubMed, EMBASE, EBSCO, and Web of Science. However, this review has some potential limitations. First, we only included observational studies rather than randomized studies, and our analysis demonstrated relevance other than causality. Second, the inclusion and exclusion criteria ablation strategies, types of AF, degrees of OSA, and even the existence of occult OSA differ among the included studies; these factors lead to heterogeneity in this meta-analysis. Nevertheless, subgroup and sensitivity analyses were performed to adjust for potential publication bias and confirm the outcome stability. In addition, a majority of the included patients were from the study by Holmqvist et al, which is the primary, original source of heterogeneity.

5. Conclusion
This meta-analysis found that OSA is a significant factor in the progression or recurrence of AF. CPAP therapy, which may be beneficial for patients with AF, may be a potential treatment for patients with AF besides medication, RFA, and direct current cardioversion.

Author contributions
MZ and WM designed the study. XYL and XBZ were involved in the selection of publications and data collection for the meta-analysis. XMX reviewed the selected studies. XYL, JD, CC, LM and JYL participated in data analysis. XYL and XBZ wrote the core manuscript, and all authors reviewed and approved of the final manuscript.

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