

# Atrial fibrillation and sleep apnoea - a review of the mechanical interplay

## EDUCATION

### AUTHOR

**Vaibhav Mishra**

St George's, University of London

*Address for Correspondence:*

Vaibhav Mishra

St George's University of London

Cranmer Terrace

Tooting, London

SW17 0RE

Email: m1500016@sgul.ac.uk

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### ABSTRACT

**Summary**

Atrial fibrillation, a chaotic and irregular arrhythmia, is occasionally encountered in clinical practice alongside sleep apnoea, a form of sleep-disordered breathing. The pathophysiological mechanisms underlying the link remain ambiguous. Together, these two conditions seem to be mutually reinforcing and significantly interfere with an individual's quality of life.

**Relevance**

Atrial fibrillation is the most common cardiac arrhythmia faced by clinicians worldwide, whilst sleep apnoea is becoming increasingly prevalent. It is important for medical students to be clinically aware of the relationship between the two as therapeutic rehabilitation of one may reduce the severity of the other and improve overall prognosis in patients who suffer from both.

**Take Home Messages**

Further research is needed to explore the synergistic relationship between atrial fibrillation and sleep apnoea and the likelihood of one complicating into the other. However, it is important to be aware of this link as it is often missed in practice, leading to deterioration of symptoms and patient anxiety.

## BACKGROUND

Atrial fibrillation is a widespread supraventricular arrhythmia characterised by irregular atrial activity as a result of abnormal conduction. (1) Sleep apnoea is a form of sleep-disordered breathing delineated as repeated cessation of breathing and/or periods of overly shallow breathing during sleep, co-existing with physiological stressors that include hypercapnia and autonomic nervous system fluctuations. (2) Atrial fibrillation and sleep apnoea are occasionally seen together in clinical practice, but the causal relationship and pathophysiological mechanisms implicated between the two remain unclear. As well as understanding the relationship between atrial fibrillation and sleep apnoea, the objective of this review is to determine whether the maintenance of normal sinus rhythm in patients with atrial fibrillation can reduce the severity of sleep apnoea, and vice versa. This is a topic of high relevance to medical students as the interplay between atrial fibrillation and sleep apnoea is often missed in university lectures that outline these conditions. This may be due to a lack of awareness of this link amongst medical professionals or perhaps due to the poor understanding of the complex mechanisms underpinning the two. Cardiology and respiratory medicine are two important specialities to which medical students are continuously exposed to through teaching and ward-based work. Understanding and recognising the relationship between atrial fibrillation and sleep apnoea will allow students to extend their studies beyond the curriculum to explore how they can improve outcomes in these patients further.

### Atrial Fibrillation

The prevalence of atrial fibrillation increases with age, affecting roughly 4% of the Western population over the age of 60. (3) Several mechanisms have been suggested for the pathogenesis of atrial fibrillation, the most popular theory being a single electrical focus or multiple foci which orchestrate irregular electrical activity throughout the atria, leading to the formation of unstable circuits and multiple wavelets that maintain each other by generating areas of slow conduction. (1) Most of such focal activity originates in the pulmonary vein where cardiomyocytes evolve pacemaker-like properties, directing abnormal calcium release and triggering automaticity which leads to increasing atrial ectopy, spontaneous depolarisation and re-entry of circuits. (4)

### Sleep Apnoea

The severity of sleep apnoea is measured using the apnoea-hypopnoea index. Apnoea is defined as the “cessation of airflow for at least ten seconds” and hypopnoea can be defined as any one of “substantial reduction in airflow (>50%)”, “moderate reduction in airflow (<50%) with desaturation (>3%)”, or “moderate reduction in airflow (<50%) with electroencephalographic evidence of arousal”. (2, 5) Sleep apnoea is subdivided into obstructive and central.

### Obstructive Sleep Apnoea

Obstructive sleep apnoea is a highly prevalent sleep-disorder characterised by repetitive interruption of ventilation during sleep, due to collapse of the upper airway resulting in an apnoea-hypopnoea index of ‘ $\geq 5$  per hour with more than 50% obstructive in nature’. (2) This leads to oxygen desaturations and frequent night-time waking with ramifications such as daytime somnolence and elevated sympathetic output. Irregularities in the anatomy of the pharynx, the physiology of upper airway muscle dilators and the stability of ventilatory control are principal causes of repetitive pharyngeal obstruction during sleep. (2) Regular arousal from sleep occurs to remedy the collapse by activating the sympathetic nervous system and hence causing fractured sleeping patterns, reduced cognitive function and quality of life. (2)

### Central Sleep Apnoea

Central sleep apnoea is characterised by an unsteady ventilatory drive leading to weakened gas exchange. It is primarily diagnosed when the apnoea-hypopnoea index is five or more per hour with more than 50% of episodes being classed as central in subset. (5) Ventilation is managed through chemoreceptors at the carotid body peripherally and through neurones in the medulla centrally. They answer to CO<sub>2</sub> via alterations in H<sup>+</sup> concentration and chemosensitivity fluctuates between healthy and unhealthy individuals. Individuals with a high chemosensitivity respond to minute changes in chemical stimuli which in turn creates unstable breathing patterns. (5)

### The Causal Relationship Between Atrial Fibrillation and Sleep Apnoea

It is approximated that 50% of patients with atrial fibrillation also have obstructive sleep apnoea. However, it is difficult to establish whether the two are mutually perpetuating due to the existence of several other risk factors such as increasing age, high BMI, hypertension, diabetes mellitus and congestive heart failure. (1) Central sleep apnoea has been shown to increase the risk of incident atrial fibrillation by 2.58-fold, especially in older men. (6) It is not well understood as to whether sleep-disordered breathing leads to the initiation and perpetuation of arrhythmogenicity or vice versa; understanding the causal relationship between the two may aid to identify therapeutic interventions and whether treatment of one can rehabilitate the other.

### Atrial Fibrillation and Obstructive Sleep Apnoea

Existing respiratory effort during pharyngeal collapse stipulates considerable decreases in intrathoracic pressure. Negative intrathoracic pressure increases cardiac preload and left ventricular afterload. (2) After the discontinuation of apnoea, an increased stroke volume alongside a vasoconstricted circulation causes repetitive increases in systemic blood pressure during night-time. Chronically, obstructive sleep apnoea consequently leads to sustained periods of increased blood pressure and ultimately hypertension. Hypertension is associ-

ated with left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement and slowing of atrial conduction velocity, all of which can initiate and maintain atrial fibrillation. (7)

One interventional cross-over study found that simulating obstructive apnoea and hypopnoea in patients produced premature atrial contractions, an important trigger for atrial fibrillation. (8) The forced inspiratory effort in resistance to a congested airway seen in patients with obstructive sleep apnoea during sleep, causes substantial sub-atmospheric drops in intrathoracic pressure. Repetition of this throughout the night misshapes the left atrial wall and induces an electrical trigger along with atrial conduction deformation. The combination of this leads to premature atrial contractions during obstructive apnoeic episodes, eliciting atrial fibrillation. A limitation of this study, however, was that sympathetic activity was not precisely measured and elucidated through observation of changes in heart rate.

Deformation and slowing of conduction was also observed in a separate study which found that obstructive sleep apnoea was related to bi-atrial structural remodelling through speckled areas of low voltage and non-typical electrograms mediated by mechanical stretch of the atrial wall and spontaneous atrial premature beats. (9) A key strength of this study was that individuals with confounding risk factors such as hypertension, obesity, diabetes mellitus and structural heart disease were excluded. Although the sample size was relatively small and there was lack of real randomisation in the trial, the results are useful as an indicator for a bigger study design.

### Atrial Fibrillation and Central Sleep Apnoea

There are strong associations between central sleep apnoea and atrial fibrillation in patients with congestive heart failure. (10) However, the relationship between central sleep apnoea and atrial fibrillation in the absence of congestive heart failure is unclear and there is limited literature analysing this. One study evaluated 60 patients with central sleep apnoea, 60 patients with obstructive sleep apnoea and 60 healthy controls, with aims to identify the prevalence of atrial fibrillation in central sleep apnoea in the absence of other cardiovascular disease. (11) The prevalence of atrial fibrillation in patients with central sleep apnoea was 16-fold higher than in the obstructive sleep apnoea group and 8-fold higher than in the control group. This demonstrates that the well-founded relation between central sleep apnoea and atrial fibrillation is not restricted to patients with congestive heart failure and can happen in its non-existence. The study hypothesised that the mechanism triggering central sleep apnoea in patients with atrial fibrillation involves irritation of pulmonary vagal irritant receptors leading to respiratory system unsteadiness, similar to the underlying link between central sleep apnoea and congestive heart failure. It is also speculated that central sleep apnoea may trigger atrial fibrillation due to chronic hyperventilation, prompting hypocapnia and ultimately impairing cardiac electrical stability. (10)

Due to the closely related confounding variables mentioned, it is difficult to pick apart the exact mechanisms associated between sleep apnoea and atrial fibrillation and whether one encourages the other. One population study aimed to differentiate the connec-

tions of obstructive sleep apnoea from central sleep apnoea with atrial fibrillation. (12) After adjusting for confounding variables, individuals with central sleep apnoea showed a 2-3-fold increase in odds of progression to atrial fibrillation. These results were homogeneous in minimally adjusted models, as well as models modified for atrial fibrillation risk factors and obstructive apnoea-hypopnoea index. However, it was observed that atrial fibrillation was under-represented in their evaluation due to its paroxysmal nature and so it may be plausible that some individuals may have been missed in the follow up. It is interesting to note that the study did not find any significant connection between obstructive sleep apnoea and atrial fibrillation based on obstructive apnoea-hypopnoea index, after adjusting the model for covariates. This is in contrast to previous studies which were able to determine a relationship between obstructive sleep apnoea and atrial fibrillation in the absence of other risk factors. (8, 9) It can be concluded that the population study above may be more reliable due to the larger sample size and the meticulously systematised collection of sleep data. (12)

### Therapeutic Interventions

Obstructive sleep apnoea, as a modifiable risk factor for atrial fibrillation, can be a suitable target for intervention in conjunction with catheter ablation, a highly effective method of rehabilitating sinus rhythm in patients with atrial fibrillation. Catheter ablation involves the passing of a thin tube via the femoral vein to the heart. The catheter is able to detect unusual electrical activity and destroy the arrhythmogenic cardiac myocytes using radiofrequency ablation. The commonest site of ablation is at the ostia (openings) of the pulmonary vein where radiofrequency lesions leave scar tissue that is unable to conduct electricity, hence eliminating the source of the arrhythmia. (13) In a prospective observational study, 251 patients with a mean age of 57.6 years and continuous atrial fibrillation were assessed to determine the link between obstructive sleep apnoea and sinus rhythm preservation, following pulmonary vein isolation. (14) 114 of these patients had obstructive sleep apnoea. The study found that the presence of obstructive sleep apnoea reduced chances of effective ablation therapy and it was suggested that screening and treatment for obstructive sleep apnoea could ameliorate the success rates of atrial fibrillation ablation. However, obstructive sleep apnoea patients were also older, had greater BMI and larger neck and waist circumferences than patients without obstructive sleep apnoea, all of which are individual risk factors for atrial fibrillation. Therefore it is difficult to establish a direct causal relationship.

The first line of treatment in both central sleep apnoea and obstructive sleep apnoea is continuous positive airway pressure (CPAP) therapy. CPAP is a form of non-invasive ventilation that works by delivering continuous pressure through a face mask to stent and stabilise the upper airway. This helps to maintain functional residual lung capacity and reduce the work of breathing. (15) CPAP therapy is used overnight in patients with sleep apnoea to ensure that the airways remain fully patent and good airflow is achieved. A 2013 study examined the role of CPAP on atrial fibrillation recurrence in obstructive sleep apnoea patients receiving pulmonary vein isolation. (16) Amongst 426 atrial

fibrillation patients sustaining pulmonary vein isolation, 62 had a polysomnography-confirmed diagnosis of obstructive sleep apnoea and 32 of these were using CPAP. The study found that 71.9% of the CPAP users remained in sinus rhythm after the first pulmonary vein isolation as opposed to 36.7% of non-CPAP users. Although there was limited collection of data displaying obstructive sleep apnoea severity, patients with obstructive sleep apnoea undergoing CPAP as well as ablation were shown to have a remarkably improved prognosis and an overall reduced arrhythmia recurrence rate. It was also suggested that patients not using CPAP may be less compliant to treatment and this may have overstated the effects of CPAP. The results of another study of 153 patients demonstrated that patients with obstructive sleep apnoea are less likely to persist in sinus rhythm following radiofrequency catheter ablation. (17) 116 of these patients were confirmed to have obstructive sleep apnoea and 82 were administered CPAP, alongside 34 without CPAP and 37 controls. CPAP treatment of obstructive sleep apnoea was related to lower recurrence rates following radiofrequency catheter ablation. Although this study further reaffirms a conclusive role of CPAP reducing atrial fibrillation recurrence following ablation, it is important to identify the limitations of this study which include the small sample size and lack of randomisation of use of CPAP. Patients with obstructive sleep apnoea were also found to have a higher prevalence of hypertension and a higher BMI.

The effective role of CPAP in patients with both atrial fibrillation and obstructive sleep apnoea was further supported in another prospective observational study which aimed to address the impact of CPAP therapy on reverse atrial remodelling by monitoring total atrial conduction time. (18) This was measured using tissue Doppler imaging intervals (PA-TDI) in patients without atrial fibrillation. Total atrial conduction time indicates atrial substrate by delay in conduction across the atria which is a reliable signal of atrial fibrillation. 55 patients were analysed and, of these, 35 had obstructive sleep apnoea and 20 were controls. Patients with obstructive sleep apnoea were found to have longer total atrial conduction time compared to healthy individuals. After CPAP therapy, the PA-TDI interval in obstructive sleep apnoea patients reduced, indicating reverse atrial remodelling and an improvement in total atrial conduction time. Despite the observed effects not being displayed in the different severities of obstructive sleep apnoea, the investigation still conveyed significant atrial remodelling reversal via CPAP treatment. There is very little research investigating the effects of CPAP in treating central sleep apnoea in atrial fibrillation, however, since the first-line treatment is the same in both obstructive and central sleep apnoea, it can be theorised that the results attained above may be transferrable to central sleep apnoea as well.

## CONCLUSION

It is difficult to establish an immediate link between atrial fibrillation and sleep apnoea due to the presence of several other common risk factors which may also contribute to atrial wall stress. The literature that has been reviewed has identified certain mechanisms implicated between sleep apnoea and atrial fibrillation. Simulation of obstructive sleep apnoea in patients without obstructive sleep apnoea has been shown to further deteriorate the arrhythmia in patients with atrial fibrillation. Alongside study models which excluded confounders, a correlation between obstructive sleep apnoea and atrial fibrillation can be inferred. However, it is difficult to reliably confirm this due to the conflicting results proposed by separate studies, which claim there is a greater link between central sleep apnoea and atrial fibrillation when compared to obstructive sleep apnoea and atrial fibrillation. There is scope for ongoing research and conduction of investigations with larger sample sizes in order to validate the current findings. The evidence showing that CPAP therapy in conjunction with catheter ablation significantly reduces risk of atrial fibrillation recurrence, in patients who exhibit both, is particularly noteworthy as it provides a foundation for amplifying the effectiveness of treatment in these patients. Continuing to develop knowledge of the apparent interdependence between these two conditions is of clinical relevance as the fabrication of further therapeutic strategies can improve the prognosis in these patients.

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