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Should targeted sleep assessment be a routine component of atrial fibrillation care?

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Take Home Messages

- Obstructive sleep apnoea (OSA) directly predisposes to the development and progression of atrial fibrillation (AF) via multiple mechanisms.
- Circa 50% of patients with AF have clinically relevant OSA.
- The presence of AF should be considered a possible direct consequence of OSA.
- AF patients with OSA do not report characteristic symptoms – typical questionnaire-based screening is ineffective and OSA should be screened for in the presence of risk factors.
- Systematic sleep evaluation should be undertaken for all patients eligible for rhythm control or with cardiovascular comorbidity such as hypertension.
- Currently, 10.8% of cardiology departments have a structured OSA pathway.
- Treatment with CPAP significantly reduces major adverse cardiovascular events, stroke, hypertension, AF recurrence and progression.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, with an estimated 1 in 3 lifetime risk and a 2.3 fold rise in prevalence is predicted[(1)]. AF is independently associated with a 1.5-2 fold increase in all-cause mortality[(2)], a 5-fold increased risk of stroke, with 15-20% of all strokes being attributed to the arrhythmia[(3)], risk of cognitive impairment (RR 1.4)[(4)], and impaired quality of life[(5)]. AF accounts for circa 1% of the NHS budget and is predicted to increase to 1.35 – 4.27% of NHS expenditure over the next twenty years[(6)].

The symptomatic benefits of early rhythm control are well established[(7)(8)(9)]. Recently, important data from the EAST AF trial demonstrated improved outcomes – HR 0.79 for major adverse cardiovascular events (95% CI 0.66-0.94) in patients managed with an early rhythm control strategy[(10)]. Whilst rhythm control using drugs and catheter ablation have been extensively investigated, they remain individual elements of a wider integrated, holistic approach to AF. Comorbidity contributes to AF incidence and progression. Most commonly, hypertension, diabetes mellitus, heart failure, coronary artery disease, chronic kidney disease, obesity, obstructive sleep apnoea and chronic inflammation[(11)]. This is reflected in the holistic, three pillar approach recommended by the ESC – The 'ABC Pathway' – A: Anticoagulation, B: Better symptom management, C: Cardiovascular and comorbidity optimisation[(12)]. The AFFIRM trial has demonstrated a significantly lower risk of all-cause mortality (HR 0.35), first hospitalisation (HR 0.65) and stroke/major bleeding/cardiovascular death (HR 0.35) for patients managed within ABC guidelines[(13)].

The ARREST-AF study demonstrated significant improvements in AF frequency, symptoms and arrhythmia free survival (RR 0.37) in AF ablation patients who underwent aggressive risk factor management[14]. Risk factor modification was an independent predictor of arrhythmia-free survival.

An increasingly recognised modifiable risk factor for AF incidence and progression is sleep quality and duration.

Sleep

Sleep involves progression through cycles every 90-120 minutes **(figure 1)**, from stage 1 to stage 4 before entering the rapid eye movement (REM) stage. REM sleep is characterised by brain activity and paralysis with high frequency eye movement and dreaming. Non-REM sleep is typified by four stages when the brain is less active but the body can move[15].

Modern life and obesity have contributed to increasing prevalence of sleep disorders. Indeed, symptoms of insomnia have been reported in 12% of adults[16] whilst sleep disordered breathing (SDB) is thought to affect 9-17% of 50-70 year olds[17].

Obstructive sleep apnoea (OSA) is the most common form of SDB and is characterised by obstruction of the upper airway, resulting in repetitive apnoeas and hypopnoeas accompanied by oxygen desaturation and arousal from sleep; it is estimated that 1.5 million adults live with the condition in the UK, and only 330,000 are currently being treated[18]. Diagnosis is typically made with an apnoea–hypopnoea index (AHI) ≥5 on a sleep study and excessive daytime sleepiness[19].

Sleep and the heart

SDB is highly prevalent in patients with AF, heart failure and hypertension and is associated with increased mortality, cardiovascular events and arrhythmia[20], whilst sleep duration, both too short (RR 1.48) and too long (RR 1.38) is associated with poor cardiovascular outcomes[21].

It is thought that over 50% of patients with AF have clinically relevant SDB[22]. The link between SDB and AF is well recognised. Kwon and colleagues[23] found that higher AHI was associated with a trend toward AF (OR 1.22) following adjustment for multiple confounders, whilst previous work has estimated an OR as high as 4.02 for development of AF[24]. Interestingly, greater slow wave sleep duration (NREM stage 4, when parasympathetic tone is highest- see figure 1) was associated with lower odds of AF in a linear fashion (OR 0.66), even after adjusting for AHI[25]. A significant inverse association between arousal index and AF likelihood was observed (OR 0.65).

Using mendelian randomisation, the relationship between AF and OSA has been shown to be causative – genetically predicted OSA was associated with an increased risk of AF (OR 1.21, 95% CI, 1.12-1.31)[26][27].

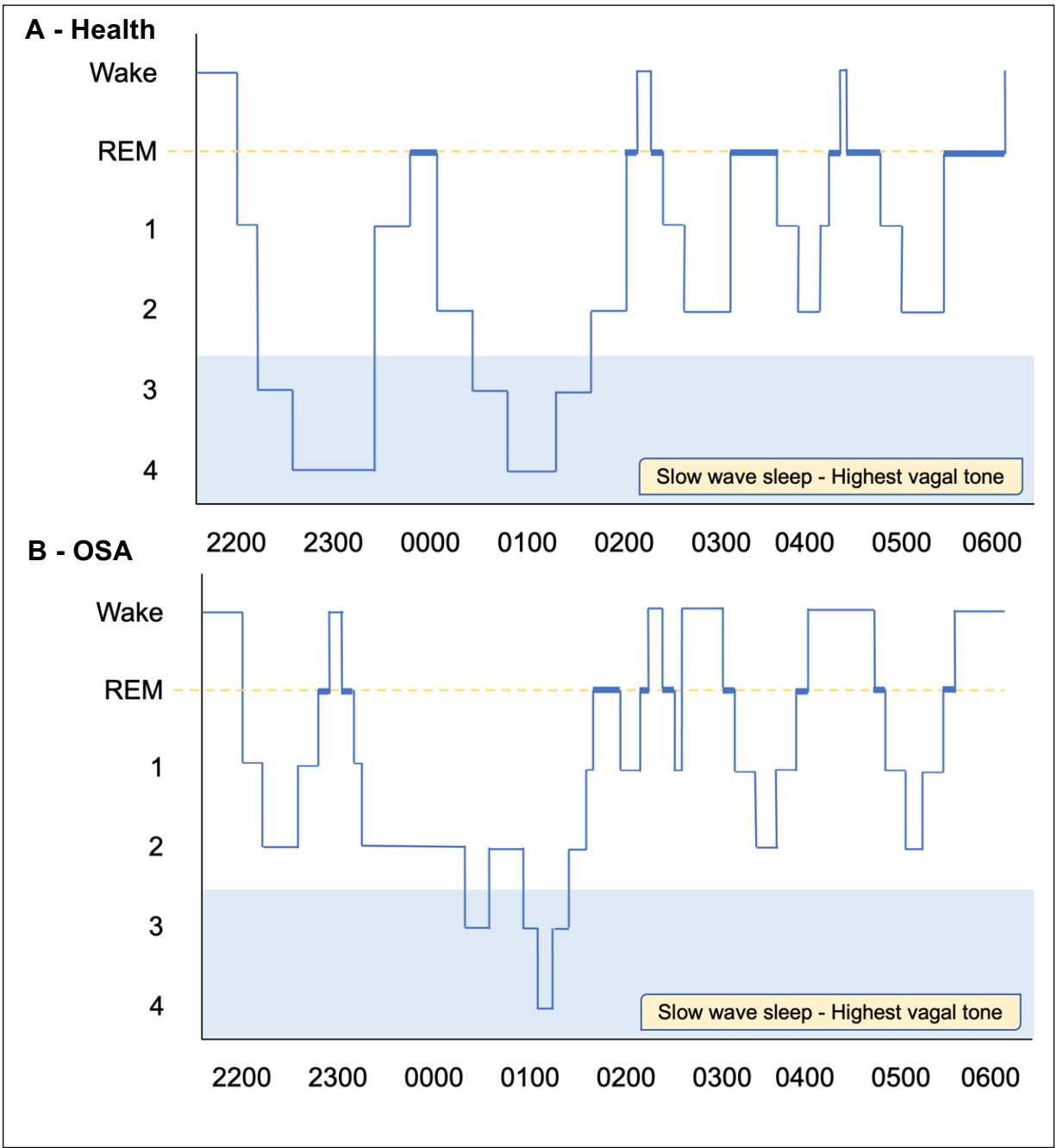

Figure 1 – Hypnograms demonstrating progression through stages of sleep. A) Normal sleep with sustained slow wave sleep initially before REM becomes more dominant. Infrequent waking. **B)** Sleep pattern in obstructive sleep apnoea. Limited slow wave sleep, frequent waking.

Mechanisms of arrhythmogenesis in OSA

Negative intrathoracic pressure

Repetitive episodes of negative intra-thoracic pressure during obstructive events are the most salient factor for the development of AF[20] (figure 2). In humans, negative intrathoracic pressure resulted in increased frequency of atrial premature contractions, potentially triggering AF[28]. Negative intrathoracic pressure also increases LV transmural pressure, increasing afterload , which leads to LV hypertrophy, diastolic dysfunction and atrial stretch[29]. Atrial stretch is also provoked directly by negative intrathoracic pressure[30] whilst cyclical fluctuation is likely to exacerbate both effects. In a porcine model, there was a significant shortening of the atrial effective refractory period, increased AF inducibility and increased blood pressure with negative tracheal pressure. These changes were abolished when repeated with atropine– suggesting parasympathetic hyperactivity[31].

Autonomic nervous system hyperactivity

In health, there is an increase in parasympathetic tone and withdrawal of sympathetic tone during NREM sleep; this then reverses in REM sleep. This cyclical pattern is disturbed in OSA, where baseline sympathetic tone is higher with impaired cyclicity due to repetitive chemoreceptor stimulation, ultimately resulting in hypertension[32]. In addition, the baro-receptor reflex resets to an elevated mean arterial pressure after only 30 minutes of intermittent hypoxia[33], increasing ventricular afterload and atrial stretch.

Mammalian models have demonstrated a close association between parasympathetic innervation and AF induced by OSA. Ablation of cardiac vagal innervation significantly suppressed AF inducibility[34] in dogs. In parallel, Linz and colleagues observed significant parasympathetic activation during negative intra-thoracic pressure, facilitating the initiation of AF[35] and a loss of AF inducibility following vagotomy in pigs[31].

Rapid excitation within the pulmonary veins is the most common electrical precipitant of AF. This is related to shortened action potential duration and early after depolarisations leading to triggered firing[36]. Elevated sympathetic tone induces a significant Ca^{2+} current which increases the likelihood of early after depolarisations via the Na^{+}/Ca^{2+} exchanger, whilst increased parasympathetic tone shortens the action potential duration and refractory period[37].

Hypoxia and inflammation

Cyclical hypoxia and hypercapnia trigger the chemo-reflex, enhancing sympathetic tone and increasing LV afterload, chronotropy and inotropy. This results in increased myocardial oxygen

demand during a shortage of supply, causing repeated cycles of myocardial ischaemia – promoting fibrosis, a known substrate for arrhythmia. Cyclical blood gas disturbance results in production of reactive oxygen species and activation of the inflammatory cascade which may produce adverse myocardial remodelling and atherosclerosis. Indeed, patients with OSA have over three times the concentration of C-reactive protein circulating compared to controls and this was independently associated with OSA severity[38]. Treating OSA with continuous positive airway pressure (CPAP) significantly attenuated this effect[39].

Obesity

Obesity is the most common link between AF and OSA. A meta-analysis of 78,602 subjects found that obese individuals had a significantly increased risk of incident AF (RR 1.49, 95% CI 1.36-1.64)[40]. Obesity exacerbates all risk factors predisposing to AF – hypertension, the metabolic syndrome, raised intrathoracic pressures, OSA, coronary disease, chronic inflammation, diastolic and dysfunction – which all lead to progressive atrial dilatation and dysfunction[41].

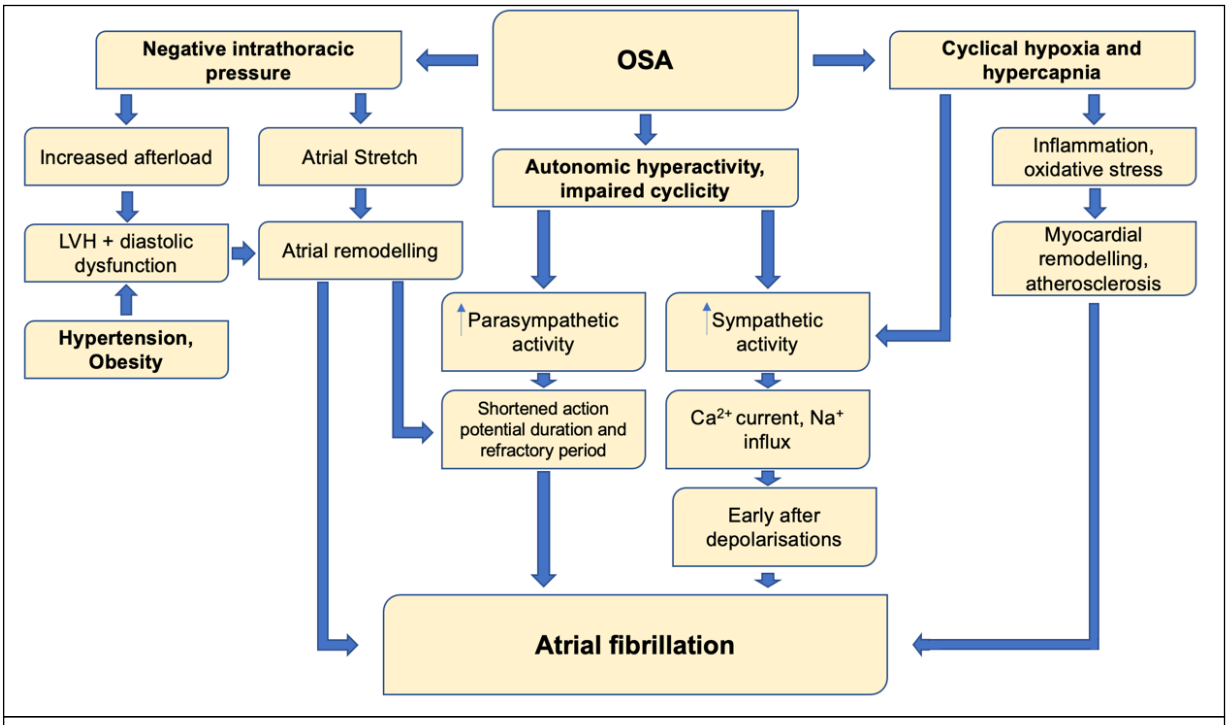

Figure 2 – Pathophysiology of obstructive sleep apnoea predisposing to AF. Negative intrathoracic pressure, obesity, hypertension, autonomic hyperactivity and cyclical blood gas disturbance all contribute.

Arrhythmia therapy implications

The presence of AF should be considered a possible consequence of sleep apnoea. AF patients with OSA are less likely to respond to anti-arrhythmic medications[33], and more likely to have AF recurrence following electrical cardioversion or catheter ablation[42][43]. In parallel, sleep disordered breathing has been shown to be an independent predictor of stroke[44] in AF patients.

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA; it splints the upper airway open and is able to mitigate many of the maladaptive effects of OSA including daytime somnolence, hypertension[45][46], cognitive decline[47], endothelial dysfunction[48] and LV systolic dysfunction[49]. From a general cardiovascular perspective, a meta-analysis demonstrated a significant reduction in MACE and stroke (RR 0.43, 95% CI 0.23-0.8) in OSA patients with CPAP adherence >4 hours per night[50].

Initially, data from observational studies demonstrated that CPAP use in OSA was associated with maintenance of sinus rhythm following cardioversion[42]. Recent meta-analysis of 14,812 patients demonstrated a significant reduction in AF recurrence and progression (RR 0.70, 95% CI 0.57-0.85)[51] in OSA patients on CPAP who were managed medically or with catheter ablation, and this was comparable to that in the non-OSA group. This was seen both in patients who underwent catheter ablation and those who were managed medically. AF recurrence and progression in the CPAP treated group was similar to that in the non-OSA group. This trend has been repeated in a recent RCT[52] and data from large, randomised RCTs may reaffirm these trends and allude to a mortality benefit.

Given the proven symptomatic advantages and emerging data on prognostic benefits of early rhythm control[10], CPAP could be an important intervention in patients with OSA and AF.

Screening

The 2020 ESC AF guidelines suggest screening for OSA before the initiation of rhythm control strategies in patients with symptomatic AF with the aim of reducing symptomatic recurrence[12]. Typically, a diagnosis of OSA is suspected in those with excessive daytime sleepiness, unrefreshing sleep, morning headaches and frequent awakening when risk factors such as male sex, obesity, advanced age, alcohol use and smoking are present[53].

Importantly, most AF patients with severe OSA do not report typical symptoms[54]. In the SNOOZE-AF study, two thirds of AF patients undergoing sleep studies had OSA, of which the majority reported low levels of daytime somnolence[55]. In addition, the presence of OSA risk factors were more predictive of moderate to severe OSA. Indeed, a meta-analysis has demonstrated that AF recurrence risk following ablation was significantly higher (RR 1.40) if OSA had been

diagnosed via polysomnography but not if OSA was diagnosed using the Berlin questionnaire. This, therefore, is not an appropriate screening tool in this setting[56].

With this in mind, systematic sleep evaluation should be offered to all patients eligible for rhythm control or with cardiovascular comorbidity such as hypertension that could be optimised to prevent MACE.

Given the frequent absence of symptomatology, there is scope for development of an arrhythmia focussed screening algorithm. The current body of evidence may not justify screening all AF patients for OSA, but perhaps a more targeted approach could be adopted where patients with OSA risk factors, difficult-to-treat AF or those considered appropriate for aggressive rhythm control undergo assessment for OSA[57][58] (**figure 3**). Novel methods of detecting these patients, such as automated screening of discharge summary coding could be trialled.

Currently, if OSA is suspected, patients should be referred to a sleep clinic for a formal sleep study, however, given many patients wait 18 weeks or more for a respiratory clinic appointment[59], home overnight oximetry organised from the cardiology clinic could be used as a pre-screening tool to rule out OSA[60]. This has an estimated sensitivity of 94.4% and a specificity of 78.9% in the absence of chronic lung disease. OSA is ruled out if there are under five hypoxia events (4% or more fall in SpO_2) per hour (oxygen desaturation index)[61].

That being said, there are barriers to implementing targeted OSA screening directly from the arrhythmia clinic including lack of appropriate reimbursement models, local infrastructure, and access to sleep assessment technology. Recent data from the European Heart Rhythm Association demonstrated underutilisation of OSA assessment with only 10.8% of cardiology departments reported as having a structured OSA assessment pathway[62]. Importantly, only 6.7% of 186 respondents indicated that they test >70% of their AF patients for OSA as part of a rhythm control strategy. Lack of established collaboration between cardiology and sleep teams and lack of financial and work-force resources were cited. An integrated model of holistic AF care with inter-departmental collaboration would mitigate many of these barriers.

For all-comers, the sleep clinic is a useful environment to undertake AF screening as the diagnostic yield will far exceed that of the general population - The ESC make a 1b recommendation for opportunistic AF screening or those ≥65 years[12].

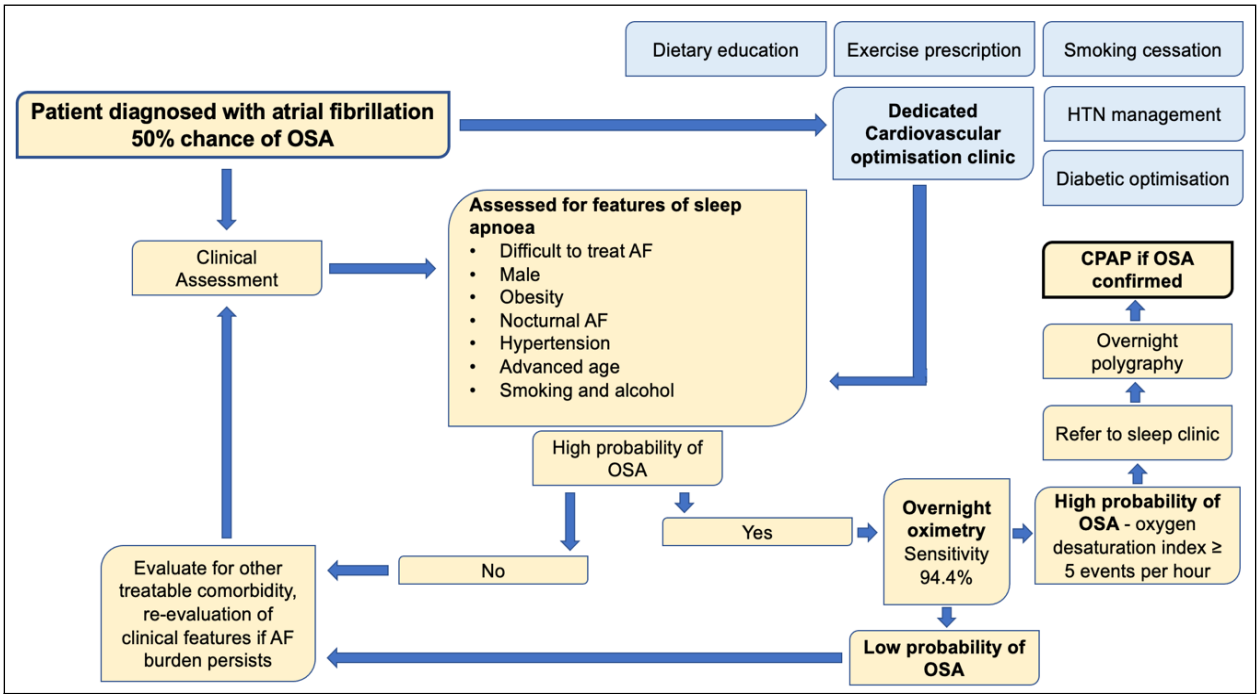

Figure 3 – Algorithm of obstructive sleep apnoea (OSA) diagnosis. Due to high prevalence and limited efficacy of anti-arrhythmic medications and catheter ablation as sole interventions, structured OSA assessment is crucial. Patients can be referred from cardiology clinic to a dedicated cardiovascular optimisation clinic where holistic care of cardiovascular risk factors is provided. Alternatively, patients can be assessed for OSA features and screened for OSA via pulse oximetry directly in the cardiology clinic. Assessment for OSA should ideally take place in any general cardiology clinic given the impact on hypertension, left ventricular systolic dysfunction and major adverse cardiovascular events.

Holistic Care Pathway

It is appropriate to assess for OSA not only in patients with AF, but in those with other cardiovascular diseases, based on accumulating evidence that CPAP (>4 hours/night) improves cardiovascular outcomes in patients with OSA and hypertension, heart failure and pulmonary arterial hypertension[63]. These patients are all likely to benefit from holistic risk factor optimisation via a dedicated optimisation clinic (**figure 3**).

From an AF perspective, the ESC guidelines do not address all those that may benefit from sleep assessment given the circa 50% OSA prevalence in the AF cohort and positive impact of CPAP on both general and cardiovascular health. Given the substantial cost of AF admissions and stroke, a business case could be formulated for an optimisation clinic (figure 3) or increased sleep clinic capacity as 25% of new patients are currently waiting longer than 18 weeks for a respiratory appointment[59].

Once patients are screened and deemed to have a high likelihood of OSA, formal diagnosis is then made using a sleep study.

Assessment

Sleep studies record physiological channels during sleep such as brain activity, pulse oximetry and body movement. Polysomnography is the gold standard but typically requires overnight stay in a sleep unit. Respiratory polygraphy measures at least four channels including oximetry, respiratory rate, apnoeas, hypopnoeas, snoring and body position and increasingly occurs in the patient's home[64]. The diagnosis and severity of OSA is based upon the AHI.

Treatment

The multi-disciplinary 'AF Team' should be responsible for management of this multi-system disorder. Typically, this would consist of a cardiologist, pharmacist, GP, dietician, sleep specialist and arrhythmia nurse who would be well placed to coordinate care. Sleep education is a necessary first step – patients frequentlya report 'getting by' on five to six hours per night, unaware of the significant health consequences[65]. Challenges such as CPAP adherence (estimated between 40-85%[66]) and tolerance should be addressed, ideally by a community team able to support the patient with self-care in their own environment. Modifications such as nasal devices, trials of positional therapy and oral devices are alternatives but with limited data[67]. In line with the ABC approach, co-morbidity should be optimised.

Conclusions

Detecting and treating OSA prevents major adverse cardiovascular events and prevents AF recurrence and progression. Current evidence supports a targeted screening approach based on OSA risk factors in patients living with AF, particularly in those undergoing rhythm control or with difficult-to-treat AF. Large prospective RCTs are needed to refine arrhythmia focussed screening and treatment algorithms. Multi-disciplinary collaboration will be fundamental to the wider roll out of OSA screening and treatment initiatives for an ever-growing population living with AF.

Disclosures

Nil

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