Heart, Lung and Circulation (2017) xx, 1–9
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2017.05.127

REVIEW

Atrial Fibrillation and Sleep Apnoea: Guilt by Association?

Zaidon Al-Falahi, MBBCh [a*], Jonathan Williamson, MBBS Bsc(Med) FRACP PhD [b], Hany Dimitri, MBBS PhD FRACP [a]

[a]Department of Cardiology, Liverpool Hospital, Sydney, NSW, Australia
[b]Department of Respiratory Medicine, Liverpool Hospital, Sydney, NSW, Australia

Atrial fibrillation (AF) and obstructive sleep apnoea (OSA) are both common, often underdiagnosed conditions with serious sequelae. An association between these two conditions has been recognised but the nature of this relationship remains a topic of active debate. Despite that lack of strong, randomised controlled trials, there is a considerable body of data indicating that not only does untreated OSA provide the substrates and triggers for AF but that OSA, itself, is also a therapeutic target for the management of cardiovascular disease in general and of AF in particular.

Keywords Atrial fibrillation • Obstructive Sleep Apnoea • Myocardial substrate • Remodelling

Background and Historical Perspective

Charles Dickens described the hypersomnolent ''fat Joe'' in his first novel ''Posthumous papers of the Pickwick Club'' in 1837 [1]. A century later, Sir William Osler coined the term ''Pickwickian Syndrome'' [2] to describe the association of hypersomnolence, snoring and obesity, but it was only in the late 1970s that the syndrome of obstructive sleep apnoea (OSA) was described in its modern form [3,4]. The term, sleep-disordered breathing (SDB) is the umbrella term encompassing all breathing disorders during sleep [5], of which OSA is the most common and will be the main focus of further discussion [6]. For years, tracheostomy was the only management option for OSA before the advent of nasal continuous positive airway pressure (CPAP) in 1981 revolutionised treatment, remaining the mainstay of therapy to this day [7–9].

When Willem Einthoven first presented an atrial fibrillation (AF) recording in 1906 from his then newly invented electrocardiogram [10,11], he probably did not realise that this supraventricular tachyarrhythmia with uncoordinated atrial activation was the most common pathological cardiac arrhythmia [12], and that it would reach epidemic proportions across the globe and contribute to significant cardiovascular morbidity and mortality [13–17].

Since the 1970s, an association between OSA and cardiovascular disease (CVD) has been recognised [18–23]. In 1998, Wilcox et al. suggested the term ''Syndrome Z'' to draw attention to the clustering of central obesity, OSA, systemic hypertension, dyslipidaemia and their interaction in promoting cardiovascular morbidity and mortality[24]. Mounting evidence now points towards cardiovascular morbidity and mortality as the most serious sequelae of OSA [25–27], leading to the suggestion that OSA is a cardiovascular disease [28–30]. The exact nature of interaction between OSA, obesity and cardiovascular disease remains a subject of active investigation and debate. Obstructive sleep apnoea sits at the intersection of multiple risk factors and contributes to several pathological pathways that promote cardiovascular diseases, including AF (Table 1).

Scope and Definitions

Obstructive Sleep Apnoea (OSA)

Obstructive sleep apnoea is a major public health concern, and while estimates of its prevalence vary, depending on

*Corresponding author at: Liverpool Hospital, Cardiology Department, Locked Bag 7103, Liverpool BC, NSW 1871, Australia. Phone 0459332103; fax: 02 8738 3054., Email: zaidoni@gmail.com

Please cite this article in press as: Al-Falahi Z, et al. Atrial Fibrillation and Sleep Apnoea: Guilt by Association? Heart, Lung and Circulation (2017), http://dx.doi.org/10.1016/j.hlc.2017.05.127

Table 1 Features of Syndrome Z and it's reference should be reference number 24 (as is alluded to in the text).

Hypertension
Central obesity
Insulin resistance
Hyperlipidaemia
Obstructive sleep apnoea

the criteria used, up to 24% of Australian men and 11% of Australian women aged ≥40 years have an apnoea-hypopnoea index (AHI) ≥15 events/hour [31]. Earlier Australian studies [32], and studies in the US, reported similar figures [33], and its prevalence has risen sharply over the past three decades [33,34], mirroring the epidemic of obesity [35], which remains by far its most important modifiable risk factor [36–38]. Despite the high prevalence, 92% of women and 83% of men with moderate to severe disease remain undiagnosed [39,40]. Other important risk factors include male sex, older age and unfavourable anatomic variations of the upper airway [34]. It is also important to recognise that not all OSA patients are obese and hypersomnolent; ethnicity may play a role in the predisposition to OSA at lower body mass indexes, such as is the case in Asian patients [41,42].

Obstructive sleep apnoea is characterised by repetitive airflow obstruction of the upper airway leading to recurrent hypopnoeas (reduction in airflow to <50% of normal) or apnoeas (complete cessation of airflow for >10s). Episodes may be associated with oxyhaemoglobin desaturation and terminated by transient cortical arousals leading to sleep fragmentation and disrupted sleep architecture [5,43]. Polysomnography (PSG) is the gold standard investigation for the diagnosis of OSA and is used to calculate the AHI — i.e., the number of apnoeas and hypopnoeas occurring per hour during sleep. The current diagnostic criteria of OSA, as set out by the American Academy of Sleep Medicine in the third edition of the international classification of sleep disorders (ICSD), requires an AHI >5 together with symptomatic sequelae such as excessive day time sleepiness as measured by Epworth Sleepiness Scale [44], morning headaches, dry mouth on waking or witnessed episodes of obstructed breathing [3,5,45]. There are multiple classifications of OSA severity, but, according to the latest ICSD edition, it is classified as mild (AHI 5-15), moderate (AHI >15-30) or severe (AHI >30) [45]. In the latest American Academy of Sleep Medicine (AASM) edition (2014), additional measures such as degree of sleepiness, extent of desaturation and the severity of associated cardiac arrhythmias [5,45] are included [46]. Most people with sleep apnoea (AHI >5) report no excessive daytime sleepiness [33,34], and even ''mild'' OSA can be associated with cardiovascular events [46,47].

Atrial Fibrillation

As mentioned previously, AF is the most common cardiac arrhythmia worldwide. Numerous pathophysiological mechanisms lead to AF. While detailed discussion of these pathways is beyond the scope of this review, some basic modern concepts must be covered to give context to further discussion. Atrial fibrillation requires two components to exist, a source of ectopic beats to ''trigger'' the arrhythmia, and a remodelled myocardium, or ''substrate'', to sustain it [48]. In addition, current evidence suggests that many cases of traditionally termed ''lone atrial fibrillation'' in otherwise ''healthy'' individuals, are, indeed, secondary to many previously unrecognised risk factors, including OSA [49,50].

There are multiple sources of triggering ectopic beats, but the muscular sleeves within the pulmonary veins are recognised as an important source of paroxysmal AF triggers and are usually isolated as the primary therapeutic strategy [51,52]. Remodelling can be considered in terms of structural and electrical changes [53]. Structural remodelling includes atrial enlargement, hypertrophy, fibrosis and myolysis, amongst other degenerative changes [54]. Electrical remodelling includes reduced myocardial calcium and potassium channels and remodelled gap junction connexin hemichannels, manifesting as changes to atrial myocardial effective refractory periods (ERP) and conduction velocities [55,56]. Ultimately, remodelling leads to anatomic and electrical heterogeneity rendering the atria prone to re-entry circuits and sustained AF [55,56]. Furthermore, regardless of the initiating mechanisms of cardiac remodelling, whether it is OSA, hypertension, ischaemic heart disease (IHD) or congestive heart failure (CHF) [48,57,58], AF can always become its own driver and a catalyst to further structural and electrical remodelling [59–62], thus, ''AF begets AF'' [63].

OSA and Atrial Fibrillation

The relationship between AF and OSA certainly goes beyond simple association, and together with shared risk factors such as obesity, their pathophysiological pathways are intricately intertwined, down to the neurohumoral and cellular levels.

There is a dose-response relationship between OSA severity and rates of incident AF in a large cohort study [64], and in the Sleep Heart Health Study, AF was more prevalent in individuals with OSA (4.8%) versus individuals without OSA (0.9%) [65]. The reverse also holds true. An earlier study by Gami et al. showed that OSA was strikingly more prevalent in patients with AF than in patients with other high risk cardiac comorbidities (49% vs 32%), and these results were reproduced in a later study by Stevenson et al. in patients with normal left ventricular function, further showing that the frequency and duration of paroxysmal AF directly correlates with the severity of OSA [66,67]. These studies and others, showed that the association between OSA and AF is independent of shared cardiovascular risk factors, and is strongest in younger individuals <65 years of age.

Further cementing the link between AF and OSA, is an important case control study by Kanagala et al., which demonstrated in patients with PSG confirmed OSA, the risk of AF recurrence at 12 months after cardioversion was remarkably

Please cite this article in press as: Al-Falahi Z, et al. Atrial Fibrillation and Sleep Apnoea: Guilt by Association? Heart, Lung and Circulation (2017), http://dx.doi.org/10.1016/j.hlc.2017.05.127