Prog Cardiovasc Dis. Author manuscript; available in PMC 2010 Mar 1.

Published in final edited form as:

Prog Cardiovasc Dis. 2009 Mar–Apr; 51(5): 411–415.

doi: 10.1016/j.pcad.2008.06.004

PMCID: PMC2782661

NIHMSID: NIHMS102746

PMID: 19249447

Sleep Disordered Breathing and Atrial Fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia in the United States, with a prevalence approaching 2.5 million persons and estimates of 10 million afflicted by the year 2050.[1] The Framingham Heart Study suggests that a forty year old has a 1 in 4 lifetime risk of developing AF. [2] The importance of AF stems from its sequelae, particularly thromboembolic stroke and heart failure (HF), and a possible increase in overall mortality. [3] Despite advances in drug and non-pharmacologic therapy, AF remains a public health problem, fueling interest in alternative avenues of treatment that may come from better management of secondary causes of AF which include hypertension, cardiomyopathy and possibly, based upon increasing evidence, sleep disordered breathing.

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Obstructive Sleep Apnea—Pathophysiologic Mechanisms

The hypothesis that obstructive sleep apnea (OSA) may be important in the pathogenesis of AF has strong physiological underpinnings. With upper airway narrowing and collapse comes persisting respiratory efforts, resulting in recurrent swings in intrathoracic pressure. The thin-walled atria may be most vulnerable to these transmural forces, which, over time, could contribute to chamber enlargement, a risk factor for AF. These forces may also be an important factor in tissue stretch and remodeling at the pulmonary vein (PV) ostia, the site believed to be the nidus from which electrical discharges propagate in AF. [1]

Instability in autonomic tone characteristic of OSA may be another key mechanism in the pathogenesis of AF. The PV ostia are known to be densely populated with both adrenergic and vagal nerves. [4] Apnea and hypoxemia activate the “diving reflex”, so named from observations of physiologic oxygen conservation by marine mammals during prolonged water submersion [5], characterized by increasing vagal tone and resultant bradycardia. It is believed that the reduced refractoriness of the cardiac conducting system during bradycardia may predispose to focal electrical discharges within the PV ostia, thereby leading to AF. [6]Animal and human studies suggest that paroxysmal parasympathetic discharges are most pronounced during rapid eye movement (REM) sleep, which, even in healthy young subjects [7] has been associated with marked bradycardia and prolonged asystolic pauses. During normal ventilation, lung expansion imparts vagolytic properties to dampen these effects [8] In OSA, on the other hand, there is attenuation of this buffer during pauses in breathing. Marked bradycardia may ensue, particularly in REM, during which longer breathing pauses and greater degrees of oxyhemoglobin desaturation are expected to occur. [9] Further suggestion of the influence of parasympathetic tone comes from the study of individuals with OSA who, on account of bradyarrhythmias, were referred for permanent pacemaker implantation and in whom electrophysiologic testing showed no evidence of disease of the cardiac conducting system. [10]

Heightened sympathetic neural activity (SNA) further adds to the milieu of autonomic instability in OSA. Surges in SNA are well described during acute upper airway obstruction, and there is good evidence for sleep stage dependent modulation, with bursts

of greater amplitude and frequency associated with REM. [11]This, particularly in conjunction with repetitive oxyhemoglobin desaturation and reoxygenation, may activate atrial catecholamine-sensitive ion channels and thereby result in focal discharges that initiate AF. [12] Evidence that individuals with OSA have chronically heightened sympathetic activity, even during the waking period,[11] might hinder pharmacologic rate-control strategies in the management of AF.

Finally, there is increasing evidence that the interplay of metabolic factors may be an important link between AF and OSA. Obesity, long recognized as a key determinant of OSA, has gained recent attention for its potential similar importance in AF. In the Framingham study, each unit increase in body mass index (BMI) conferred a further 4% risk of development of incident AF, an effect that appears to be mediated by left atrial enlargement. [13] A study of echocardiographic measures showed that obese subjects with OSA have higher left atrial volume indices than BMI-matched controls without OSA. [14] Other population-based studies have shown a similar correlation between AF and obesity. [15, 16] The striking increase in the prevalence of obesity in Olmsted County, Minnesota over the past 20 years has paralleled that of AF. [17]The strength of the evidence suggests these findings are likely more than coincidental, and that OSA may be an important mediator in the relationship between AF and obesity.

Systemic inflammation may also underlie the relationship between OSA and AF. Some [18] (though not all[19]) case-control studies have shown an increase in serum levels of C-reactive protein (CRP) in those with OSA. There is also evidence to suggest that inflammation may be a risk factor for AF, where elevations in CRP have been found to be associated with both new-onset and recurrent arrhythmia. [20]

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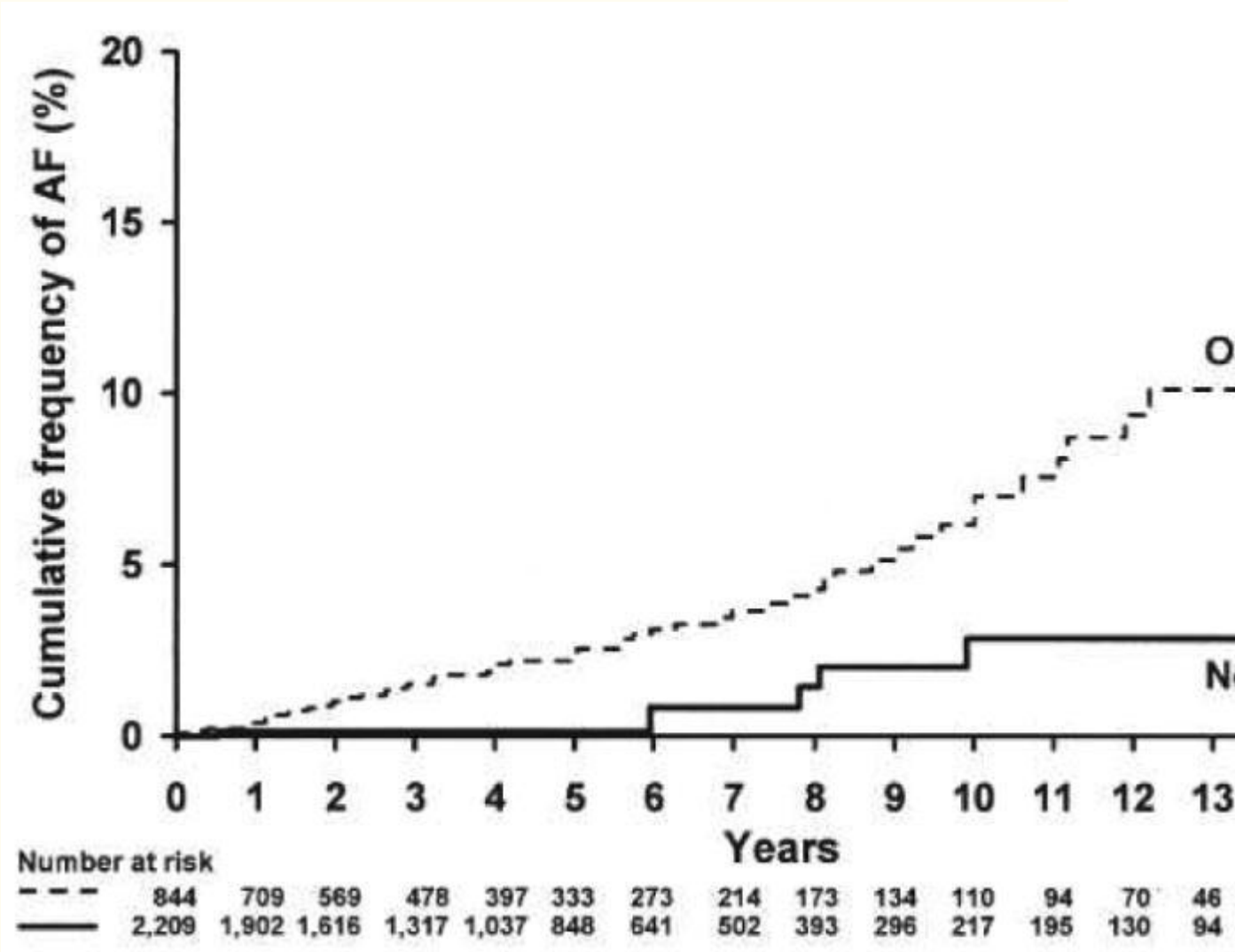
Epidemiology—Observational Studies

Although overall few in number, some observational studies, mostly case control and cross-sectional samples, have reported a frequent co-existence of AF and sleep disordered breathing (SDB). Guilleminault and colleagues, in an uncontrolled study, described nocturnal arrhythmias in a broad group of patients (mostly men) with often severe OSA, were among the first to report on the relationship twenty-five years ago. [21] With the use of 24-hour ambulatory electrocardiographic monitoring, they reported a prevalence of nocturnal paroxysms of AF of more than 3%, well above the general population prevalence of 0.4 to 1%. A more recent study, using an internally validated questionnaire assessing OSA risk, compared the prevalence of OSA in 151 consecutive patients undergoing electrical cardioversion of AF with 463 consecutive patients without AF being evaluated in a general cardiology practice.[22] While both groups were well-matched for age, sex, BMI, and prevalent hypertension and heart failure, those with AF had a significantly higher risk of OSA (49% vs. 33%), with multivariate analysis demonstrating a strong independent association between OSA risk and AF (odds ratio 2.2). The largest study published to date, a sleep referral-based retrospective cohort numbering >3,500 patients, analyzed the incidence of new-onset AF up to 15 years after diagnostic polysomnography.[23] OSA and multiple measures of its severity, in addition to the usual clinical predictors, were significantly associated with incident AF. In individuals less than 65 years of age, the decrease in nocturnal oxygen saturation (and not AHI) was an

independent predictor or incident AF. (Figure) The only population based assessment thus far published is an overnight oximetric analysis of a cohort of Japanese men which showed a correlation between the number of oxygen desaturation events and AF. [24]



Figure

Incident atrial fibrillation (AF) in subjects < 65 years of age with and without obstructive sleep apnea (OSA) during an average 4.7 years of follow-up. p=0.002. From Gami et al, 2007.

It is of interest that, in a number of these studies, measures of oxyhemoglobin saturation levels were found to be important predictors of the presence of AF. Whether this reflects underlying clinically occult cardiopulmonary disease or is a surrogate of obesity is not clear, although it is possible that the frequency-based AHI metric is a less sensitive indicator of arrhythmogenic risk in OSA.

Notably, some papers, from early descriptions to a more recent large cohort, failed to either discern or report a distinction between OSA and central sleep apnea (CSA). This discrimination is potentially important, however, since OSA and CSA, while not uncommonly co-existent, are pathophysiologically distinct disorders. Because CSA is believed to frequently result as a consequence of cardiac dysfunction, the association between CSA and AF may be mediated (or confounded) in some instances by the presence of heart failure (HF), which itself is tightly linked to AF. Sin and colleagues, in their polysomnographic assessment of 450 men and women with HF, found AF to be more tightly associated with CSA than OSA. [25] Furthermore, a recent case report provides evidence for a bi-directional relationship between CSA and AF, with the onset of CSA following a paroxysm of AF, presumably on the basis of acute deterioration in cardiac function associated with arrhythmia onset. [26] A notable exception to the hypothesis that cardiac dysfunction is important in the interaction between AF and CSA comes from Leung and colleagues, who showed a high prevalence of AF in those with idiopathic CSA and free of overt HF. [27]

In a case control polysomnographic study of ambulatory men with HF, Javaheri found AF to be significantly associated with SDB, although the majority of subjects with SDB were identified as having CSA; the proportion of those with AF and OSA was not reported. [28] Recent data from the Sleep Heart Health Study (SHHS), the largest cross-sectional sample to date to assess the prevalence of arrhythmias in SDB, did not distinguish specifically between OSA and CSA. [29] Based on expected prevalence, one may assume that most had obstructive sleep apnea, although the 4% rate of HF in the exposed group raises the possibility of CSA. In a comparison between those with a respiratory disturbance index (RDI) of 30 or more per hour (the “exposed” group) and those with an RDI of < 5/h (the “unexposed” group), the 4.8% prevalence of AF in the exposed group was significantly higher than that in the unexposed group (0.9%). [29]

A few papers suggest that OSA may mediate AF related post-cardiac procedures. Sleep studies performed in 121 patients prior to coronary artery bypass graft surgery showed that SDB predicted an approximate two-fold higher incidence of post-operative AF requiring intervention compared to a control group without SDB,[30] a finding that may explain a reported link between obesity and post-cardiac surgery AF. [31] One-year recurrence of AF following electrical cardioversion was higher in patients with untreated OSA (to the extent that they were found to be non-compliant with CPAP therapy) compared to a control group in whom polysomnography was not performed (82% vs. 53%).[32] OSA has been found to be an independent risk factor for acute failure of pulmonary vein isolation in patients undergoing radiofrequency ablation treatment for AF [33], suggesting OSA-related alterations in atrial anatomy or remodeling of electrical pathways.

It should be noted that a few epidemiologic studies have failed to show a definite association between OSA and AF. In the aforementioned study of a HF population by Sin et al, the rate of AF in those with OSA was not significantly different than in those without SDB. [25] Polysomnographic assessment of a cohort with lone AF showed a high prevalence of OSA (32%), though not substantially different than that found in a control group without AF (29%). [34] Caution should be used in drawing firm conclusions from this study, however, since the control group was comprised of a probability sample of snorers referred to a sleep lab.

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Epidemiology—Interventional Trials

These study results, while not always consistent, suggest a compelling association between OSA and AF, thereby raising the possibility of a causal relationship between the two disorders. The methodologies behind these studies, however, preclude such firm conclusions, as biases and confounders are inherently hidden in these observational reports with relatively small sample sizes. Long-term prospective longitudinal cohort studies and controlled interventional trials typically provide the highest level of evidence implicating risk factor causality in disease.

A well-executed prospective longitudinal cohort study would require that a huge sample of subjects free of AF undergo polysomnography at baseline and undergo several years of close follow up to control for co-variates. In the absence of such an expensive and resource-intensive project, which is unlikely to ever come to pass, the real question is whether or not such a risk, if present, is modifiable—a question that can only be answered with interventional trials. At present, such trials are currently sorely lacking. There is a strong possibility that treatment of OSA with CPAP, which has been shown to reduce or abolish many of the putative mechanisms that may link OSA to AF, including hypoxemia,[11] inflammation,[35] sympathetic overactivity, [11] and hypertension,[36, 37] can have beneficial effects in the setting of AF.

To our knowledge, only two published papers have reported on OSA treatment effects in AF. Guilleminault reported that, following tracheostomy in 10 subjects with severe OSA and pre-existing AF / atrial flutter, there was no observed recurrence of arrhythmia over the ensuing 6 months of follow up. [21] In the only study to date to specifically investigate the effects of OSA therapy on AF, Kanagala and colleagues compared the recurrence of AF one year after electrical cardioversion in 12 OSA patients with effective CPAP therapy, 27 patients with untreated OSA, and 79 patients with unknown OSA status.[32] AF recurred in only 42% of OSA patients effectively treated with CPAP, compared to AF recurrence in 82% of untreated OSA patients. Interestingly, the recurrence in treated OSA patients was even lower than that in the control group of AF patients (53%), possibly because this latter group included patients with undiagnosed OSA. OSA patients without recurrence were 3 times more likely to have used effective CPAP therapy than patients with AF recurrence, and no differences existed between those with and without recurrence with regard to age, gender, BMI, or hypertension. Of course, while the usual caveats pertaining to un-measurable effects of treatment non-compliance apply, these findings raise the tantalizing possibility that CPAP treatment of OSA may substantially impact important outcomes in the management of AF. Further high level studies will be needed to confirm these results before firm recommendations can be made for the routine evaluation of AF patients for OSA.

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Footnotes

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