Should we treat any sleep apnea in patients with atrial fibrillation?

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Prevalence of sleep disordered breathing in patients with atrial fibrillation

Sleep disordered breathing (SDB) is common in patients with atrial fibrillation (AF). However, there is a large variability in the reported prevalence of SDB and the exact prevalence remains unknown. The prevalence of SDB ranged between 9 and 49% in the general population and between 59 and 76% in patients with AF [1–5] (Table 1). A recent study by Strotmann et al. [6] confirms the high prevalence of SDB in patients with AF and preserved left ventricular ejection fraction. In 211 consecutive patients with AF (146 men; age 68.7 ± 8.5 years), only 6.6% of patients had no SDB [apnea-hypopnea index (AHI) $< 5/h$] and 60% of patients had moderate-to-severe SDB (AHI $\geq 15/h$), of whom the majority had coexisting obstructive and central sleep apnea (OSA and CSA). This study reports the highest prevalence of SDB in a population of patients with AF [6]. All available prevalence estimates of SDB in AF patients, are based on analyses of cross-sectional studies. Prospective longitudinal population-based studies evaluating the association between untreated OSA and incident AF are currently not available.

There are several factors that can influence the determination of the prevalence of SDB: (1) the device used to diagnose SDB, (2) the thresholds and scoring rules to determine severity of SDB as well as (3) selection bias may contribute to the large variability in the prevalence of SDB in the literature. First, the gold standard to diagnose SDB is polysomnography (PSG), which can be either performed

in-laboratory, technician-attended (level I) or unattended outside of the laboratory (level II). Portable polygraphy devices (PG) recording airflow, respiratory effort and oxygen saturation (level III) can be used to diagnose and characterize SDB. Although PG is validated against PSG in some subgroups of patient, the diagnostic accuracy of PG in AF patients is unknown. Second, different studies used different thresholds for the diagnosis of SDB. Generally, SDB is considered mild when the AHI is 5–15/h, moderate when AHI is 15–30/h and severe when the AHI is $> 30/h$. The AHI-threshold used for the diagnosis of SDB in the various studies investigating the prevalence of AF ranges between 5/h and 15/h. Third, most studies included mainly patients with paroxysmal AF. Stevenson et al. [3] showed, that the prevalence of SDB increases with the progression of AF from paroxysmal to persistent and longstanding persistent AF. Therefore, an overrepresentation of persistent AF patients might contribute to an unexpected high prevalence of SDB.

Characterization of sleep disordered breathing in patients with atrial fibrillation

Respiratory events can be classified into obstructive, central or mixed apneas and hypopneas according to the presence, absence or emergence of thoraco-abdominal movements (indicative of respiratory effort) over the course of the event [7–9]. In contrast to previous studies, Strotmann et al. found that predominant OSA ($\geq 80\%$ obstructive events) was present just in a minority, namely in 15% of AF patients. In the remaining AF population, 10% had central sleep apnea ($\geq 80\%$ central events) and 36% had coexisting OSA and CSA ($> 20\%$ obstructive events and $> 20\%$ central events) [6]. Of those with moderate-to-severe SDB 34% fulfilled the criteria for Cheyne-Stokes respiration (three successive episodes of central apneas and/or hypopneas connected by a crescendo-decrescendo variation in breathing amplitude with a cycle length of ≥ 40 s) [10].

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Table 1 Prevalence of sleep disordered breathing in the general population and patients with atrial fibrillation

Study, year (Ref.)	Source of patients	Population	Patients (n)	Prevalence of SDB (%)	SDB diagnosis	AHI threshold
Young et al. 1993 [1]	Wisconsin Sleep Cohort Study	General population	602	Female 9 Male 24	PSG	5/h
Heinzer et al. 2015 [2]	HypnoLaus	General population	2121	Female 23.4 Male 49.7	PSG	15/h
Stevenson et al. 2009 [3]	Arrhythmia centre	Controls	45	38	PSG	15/h
		AF	90	62		
Naruse et al. 2013 [4]	PVI cohort	AF before PVI	249	76	PSG	5/h
Fox et al. 2016 [5]	ECV cohort	AF before ECV	138	92	PG	5/h
				64	PG	15/h
Strotmann et al. 2018 [6]	Arrhythmia/ECV center	Majority persistent AF	211	93	PG	5/h
				60	PG	15/h

SDB Sleep disordered breathing, AF atrial fibrillation, Ref. reference, ECV electrical cardioversion, PVI pulmonary vein isolation, PSG polysomnography, PG polygraphy, AHI apnea hypopnea index

Which sleep apnea should be treated in patients with atrial fibrillation

The available clinical evidence for treatment of SDB in AF patients is poor. Meta-analyses of observational studies with a total of around 1000 patients have shown that patients with OSA have a 31% greater AF-recurrence rate after AF catheter ablation [11]. Non-randomized, observational studies suggest, that treatment of OSA by chronic positive airway pressure (CPAP) therapy can help to maintain sinus rhythm in AF patients with OSA. In patients with OSA and AF undergoing catheter ablation ($n=62$), CPAP therapy was associated with a higher AF-free survival rate at twelve months after the procedure (71.9 vs. 36.7% without CPAP) and almost similar to patients without OSA [12]. Interestingly, in this study, AF-recurrence in OSA patients treated by CPAP without catheter ablation was comparable to the AF-recurrence after catheter ablation in CPAP non-user OSA-patients [12]. In a meta-analysis of seven prospective cohort studies with a total of 1087 patients, the use of CPAP in patients with AF and concomitant predominant OSA was associated with a significant reduction in AF-recurrence by 40% [13].

Based on this data, current international AF-guidelines [14] recommend that consideration should be given to elicit clinical symptoms and signs of OSA and CPAP treatment to reduce AF-recurrence and improve AF treatment-results (for both: Class of evidence “reasonable to perform”, Level of evidence “moderate quality”). Importantly, the current AF-guidelines [14] just focus on OSA. Strotmann et al. [6] show that the majority of patients with AF may have coexisting OSA and CSA or Cheyne–Stokes respiration which might have relevant clinical implications, because it may influence the type of positive airway

pressure therapy applied [7–10]. No treatment recommendations for AF patients with SDB other than predominant OSA are mentioned in the current AF-guidelines [14].

Additionally, meta-analyses evaluating the risk of AF-recurrence after catheter ablation cannot provide a certain AHI-threshold for OSA, that indicates an increased risk of AF-recurrence. Thus, there is no consensus on which AHI threshold or other SDB severity parameter should be used to trigger CPAP initiation and guide CPAP therapy in AF patients. Current guidelines for the treatment of SDB in the general population recommend treatment when AHI is $\geq 15/h$ regardless of the presence or absence of apnea-related symptoms [15]. However, in cases of mild sleep apnea ($AHI \leq 15/h$) without symptoms treatment indication is more uncertain and these thresholds and goals of SDB treatment may not be entirely applicable to the population of AF patients. In the general population, treatment of SDB is classically initiated to reduce neuro-behavioural impact of SDB such as daytime sleepiness. In accordance with previous studies, AF patients in the study by Strotmann et al. [6] rarely reported excessive daytime sleepiness, irrespective of the severity of SDB. The burden of symptoms due to AF may often obscure and confuse those of SDB [7, 8]. Although SDB related symptoms improved, CPAP treatment failed to reduce cardiovascular events and death in patients with high cardiovascular risk and OSA in a large randomized controlled trial, [16] a finding which is confirmed by a recent meta-analysis [17]. These findings do not support routine CPAP treatment with the goal of prevention of cardiovascular events and death in patients without sleep related symptoms. In the absence of daytime sleepiness, the goal of SDB management in AF patients is to ameliorate the adverse effects of repetitive respiratory events on the atrium and to prevent the progression of AF, particularly in patients where rhythm control is the primary goal. Clinical

and preclinical studies suggest, that in addition to hypertension, obesity and metabolic syndrome, obstructive respiratory events can lead to a progressive structural remodeling process in the atrium and acute apnea associated electrophysiological create a dynamic and complex substrate for AF [7, 8, 18, 19]. From a pathophysiological point of view, early initiation of CPAP treatment makes sense to prevent the progression of the AF substrates. Evidence from randomized controlled trials of CPAP in patients with OSA and hypertension shows, that CPAP reduces arterial blood pressure most effective in patients with severe OSA with daytime sleepiness [20–22]. The same may also account for the effects of CPAP in patients with AF and concomitant OSA. Aggressive risk factor modification helps to maintain sinus rhythm and reduces recurrence of AF after catheter ablation [23–25]. CPAP treatment of severe OSA was one important component in the applied risk factor modification protocol [23–25]. Whether treatment of SDB, without targeting concomitant risk factors, which are highly prevalent in SDB patients, can prevent progression of AF or reverse structural remodeling processes in the atrium is unknown.

Conclusions

Breathing during sleep is often abnormal, particularly in patients with AF. Based on observational non-randomized studies, OSA screening and treatment is recommended in international AF guidelines [11–13]. Still it remains unclear, which AHI-threshold or additional SDB parameter should trigger and guide treatment of SDB in AF patients. The prevention of AF-recurrence may be more likely, when severe SDB and SDB with concomitant symptoms is treated. Additionally, it is unknown, whether CPAP treatment alone, without targeting concomitant risk factors, can help to maintain sinus rhythm and whether CPAP treatment can reverse the atrial arrhythmogenic substrate once it has been established in patients with more progressed persistent AF. Currently, patients are being recruited in multicenter prospective randomized controlled trials to investigate the impact of CPAP on AF burden in patients with predominant OSA (Trial-ID: ACTRN12616000262404, ACTRN12616000903482 and ACTRN12616000088448). Strotmann et al. [6] add important information about the phenotype of SDB in AF patients and show: The majority of AF patients may not have OSA, but coexisting OSA and CSA with and without Cheyne–Stokes respiration, which cannot be effectively treated by CPAP in all patients. Whether treatment of SDB other than OSA helps to maintain sinus rhythm and improve treatment outcomes in AF has not been tested and warrant further study before it can be introduced as a part of the treatment of AF in the clinic.

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