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Personalized management of sleep apnea in patients with atrial fibrillation: An interdisciplinary and translational challenge

Sleep apnea is present in approximately 70% of patients with atrial fibrillation (AF), and most AF patients diagnosed with sleep apnea show predominant obstructive sleep apnea (OSA) [1]. Treatment of OSA in AF patients by continuous positive airway pressure (CPAP) can help maintain sinus rhythm after electrical cardioversion, improve catheter ablation success rates and/or reduce the needs for medications [2]. Therefore, the European Society of Cardiology (ESC) 2020 guidelines for the management of AF recommend screening for OSA as part of a comprehensive assessment of concomitant risk factors in AF management, in which treatment of OSA may be considered to reduce AF incidence, progression, recurrences, and symptoms [3]. While many studies show an association between OSA and AF, the link between central sleep apnea (CSA) or Cheyne Stokes Respiration (CSR) and AF is less established and might be mediated by many confounders, including heart failure and comorbidities [4,5]. Moreover, a cross-ethnic comparison of the association between CSA/CSR and AF has not been conducted yet.

In this issue of the IJC Heart & Vasculature, Anzai et al. performed a cross-sectional analysis using two large population studies: [6] The Kuakini Honolulu-Asia Aging Study, a longitudinal cohort study of Japanese-American men living in Hawaii, and the Osteoporotic Fractures in Men (MrOS) Sleep Study, a longitudinal cohort study of White-American men in the U.S. After adjustment for reported concomitant conditions, CSA and CSR were both associated with higher odds of AF in Japanese-Americans and in White-Americans.

Although this study shows a clear association between CSA/CSR and AF, the causal relationship is unclear. Apneas induce hypoxia with intermittent arousal, fluctuating levels of carbon dioxide, enhanced sympathetic/neurohormonal activation and oxidative stress causing low grade inflammation [1,5]. However, experimental data supporting the arrhythmogenic role of these consequences of apneas mainly come from preclinical or clinical mechanistic studies focusing on OSA. Whether all these potential arrhythmogenic mechanisms observed in OSA can be projected to the scenario of CSA requires direct demonstration. Cardiovascular and autonomic nervous system respons to central respiratory events may differ significantly from the respons to obstructive respiratory events. Although changes in blood gas are present in both obstructive and central respiratory events, intrathoracic pressure swings during ineffective inspiration against an occluded upper airway occur only in OSA. This is despite the fact that there is an overshoot of ventilation during the crescendo phase of CSR [5]. Negative intrathoracic pressure has been shown to be associated with a combined sympatho-vagal activation leading to transient atrial and ventricular electrophysiological changes, potentially contributing to atrial arrhythmogenesis [7,8]. Another difference is the temporal relationship between autonomic nervous system activation and a respiratory event [9]. While sympatho-vagal activation is frequently observed during apneas in OSA patients, sympathetic over-activation mainly occurs during increased breathing efforts in the phase of hyperventilation and hyperpnea between central apneas in CSR [9].

Cardiovascular and autonomic nervous system responses to obstructive versus central apneas are not captured within the current assessment of sleep apnea. The apnea-hypopnea index (AHI) metric, which is used clinically to diagnose sleep apnea and assess sleep apnea severity, does not incorporate typical sleep apnea-related arrhythmogenic mechanisms, such as autonomic nervous system activation and hypoxemic burden [10–13]. Theoretically, an arrhythmia mechanism-tailored assessment of sleep apnea, incorporating several AF mechanisms, particularly the central and obstructive apnea related arrhythmogenic changes during sleep, could result in a more effective and personalized selection of AF patients who may benefit from sleep apnea treatment than the traditional approach [10]. To develop an arrhythmia mechanism-tailored assessment of sleep apnea, a combination of mechanistic studies, comprehensive signal analysis of formal sleep studies in AF patients is required. Such targeted intervention require an infrastructure redesign in which comprehensive and translational care and research can be integrated, and where treatment preferably will be delivered by an interdisciplinary team consisting of, e.g. electrophysiologists, heart failure specialists, sleep specialists, as well as nurses and allied professionals, tailored to the patient's individual situation and care needs [14]. AF-clinics following such an integrated approach have demonstrated to improve guideline adherent therapy and to have a significant impact on hospitalisation and mortality in patients with AF [15].

CSA, particularly CSR, are common comorbidities of heart failure, renal failure and stroke populations but rarely present in other cardiometabolic conditions [1]. Additionally, up to 5% of OSA patients sometimes convert to CSA once treatment CPAP has commenced (emergent CSA) [1,16]. Also, it has been shown that heart failure patients with reduced ejection fraction may shift from OSA to CSA over the course of a single night, possibly as a consequence of progressive deterioration of cardiac failure hypocapnia and a lengthening of circulation time [17]. Therefore, the presence of

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CSA and CSR should always trigger a detailed heart failure workup and consequent clinical management, as CSA/CSR may often be a consequence of underlying untreated heart failure [16]. Importantly, in the study by Anzai et al. [6] the presence and diagnosis of heart failure was solely ascertained by a questionnaire interrogating clinical signs of heart failure. Heart failure contributes to AF. Hence, the fact that heart failure was not systematically assessed in the CSA/CSR group likely explains the strong association between CSA/CSR and AF, even after adjusting for concomitant conditions.

If CSA/CSR remains present even after management or exclusion of heart failure, it is unclear which type of CSA requires to be treated in AF patients. Adaptive servo ventilation (ASV) is considered to be the most effective strategy to suppress predominant CSA/CSR [5]. However, treatment of CSA/CSR by ASV in the "SERvo VEntilation in patients with Heart Failure and increased the secondary endpoint of CV mortality by 34% reduced ejection fraction (SERVE-HF)" trial resulted in an increase in all-cause and cardiovascular mortality [18]. Therefore, ASV should not be initiated in patients fulfilling the inclusion criteria for SERVE-HF (symptomatic heart failure (NYHA class II–IV), left ventricular ejection fraction <45%, and predominant CSA/CSR). However, ASV remains indicated for patients with preserved ejection fraction and some recent cluster analyses have demonstrated that beyond the SERVE-HF population some subgroups of patients benefit from ASV in terms of reduction of hospitalisations and mortality [19]. Besides ASV, other CSA treatment strategies, such as transvenous phrenic nerve stimulation, may be considered [5]. Large randomized controlled studies investigating the effect of CSA/CSR treatment on AF outcomes are not available.

In addition to the uncertainty of how to efficiently manage sleep apnea in AF patients, the limited access to sleep apnea testing devices further complicates the implementation of sleep apnea testing and management in AF outpatient clinics. A recent joint survey by the European Heart Rhythm Association (EHRA) and the Association of Cardiovascular Nurses and Allied Professions (ACNAP) showed a clear underutilization of OSA management in AF patients [20]. Only 10.8% of cardiology departments reported to have a structured OSA assessment pathway implemented at the cardiology department, and only 6.7% of the respondents indicated that they test >70% of their AF patients for OSA as a component of rhythm control therapy. Additionally, this survey identified various structural barriers currently preventing optimal implementation, including the absence of established collaboration between cardiology and sleep clinics (35.6%), as well as the lack of financial (23.6%) and workforce-related resources (21.3%). All these factors limit structured testing facilities of OSA which currenty only occurs in a minority of AF patients. An interdisciplinary guide providing hands-on instructions to implement sleep apnea management in AF outpatient clinics would be crucial to improve comprehensive care delivery.

What are the key learnings and the take-home message for sleep apnea management of our AF patients? Systematic sleep apnea screening will identify predominant OSA in approximately 70% of all AF patients referred for rhythm control management [1]. This is crucial given that OSA treatment is recommended as an important component of combined risk factor management by current AF practice guidelines [3]. Although Anzai et al. show that CSA/CSR is associated with higher odds of AF [6], current guidelines do not recommend management of CSA/CSR in AF populations at this timepoint [3]. In the case of predominant CSA/CSR in AF patients, the initial work-up should mainly focus on managing heart failure and other clinical or sub-clinical comorbidities. It remains unclear whether and how to treat CSA/CSRdespite optimal management of concomitant comorbidities. An arrhythmia mechanism-tailored assessment of sleep apnea incorporating several AF risk factors, particularly the central and obstructive apnea related arrhythmogenic changes during sleep, can result in a more effective and personalized selection of patients profiting from sleep apnea treatment in the future.

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Disclosures

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Declaration of Competing Interest

None.

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