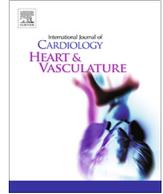




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Editorial

Central sleep apnea in atrial fibrillation: Risk factor or marker of untreated underlying disease?



Obstructive sleep apnea (OSA), the most common clinically significant breathing abnormality during sleep is prevalent in up to 70% of patients with atrial fibrillation (AF) [1–4]. Data from non-randomized studies in patients with AF suggest that treatment of OSA by continuous positive airway pressure (CPAP) may help to maintain sinus rhythm after electrical cardioversion and improve catheter ablation success rates [5]. Accordingly, screening for OSA as part of the comprehensive assessment of concomitant risk factors in AF management, is recommended in the 2020 AF guidelines of the European Society of Cardiology and treatment of OSA may be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms [6]. Whilst the relationship between OSA and AF has been established, the pathophysiological link between central sleep apnea (CSA) or Cheyne Stokes respiration (CSR) and AF is less clear. Accordingly, CSA/CSR is not mentioned and no specific treatment recommendations are included in the current AF guidelines [6]. This is, why the article by Sanchez et al. published in this issue of the IJCV is of great importance [7].

Sanchez et al. reviewed available data on the association between CSA and AF and potential pathophysiologic mechanisms of AF occurrence in patients with CSA [7]. Several mechanisms including apnea-induced hypoxia with intermittent arousal, fluctuating levels of carbon dioxide, enhanced sympathetic/neurohormonal activation and oxidative stress causing inflammation, which may be involved in AF occurrence and progression in patients with CSA, are discussed. Although all of these mechanisms have individually shown to be arrhythmogenic and may occur in patients with CSA, experimental data supporting the arrhythmogenic role mainly come from preclinical or clinical mechanistic studies focusing on OSA [1,8,9]. Whether it is possible to project and translate all these arrhythmogenic mechanisms observed in OSA directly to the scenario of CSA is questionable. Cardiovascular responses to central respiratory events may differ significantly from responses to obstructive respiratory events. While obstructive respiratory events are mainly caused by mechanical obstructions of the upper airway during sleep, central apneas are caused by central dysregulation of respiratory control and are characterized by periodic episodes of hyper- and hypoventilation resulting in intermittent changes in tidal volume and CO₂. Although changes in blood gas is related to both, obstructive and central respiratory events, intrathoracic pressure swings during ineffective inspiration against an occluded upper airway only occur in OSA. Negative intrathoracic pressure has been shown to be associated with a combined sympatho-vagal activation (diving reflex) which leads to transient

atrial and ventricular electrophysiological changes which can contribute to atrial arrhythmogenesis [9]. In comparison, similar electrophysiological changes were not observed during simulated central apneas with comparable drops in oxygen saturation, but without intrathoracic pressure changes [9]. Additionally, post-apneic blood pressure rises and activation of the circulating renin angiotensin system seem to be more pronounced with simulated repetitive obstructive respiratory events than with central apneas, as demonstrated in a pig model with simulated sleep apnea [10]. Another difference is the timing of autonomic nervous system activation in relation to a respiratory event. 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 during CSR. These observations suggest, that arrhythmogenic mechanisms identified in OSA should not be simply projected to the scenario of CSA/CSR. Importantly, recent studies even suggest beneficial and protective effects of CSR [11]. Therefore, a more detailed assessment of pathophysiological, hemodynamic and arrhythmogenic responses to central respiratory events and CSA/CSR are required, before the definite role of CSA/CSR for AF mechanisms can be defined.

How should we interpret and manage CSA and CSR in our AF patients? [1] CSA, and in particularly CSR, is often a common comorbidity of heart failure, renal failure and stroke population and rarely present in the remaining population. Additionally, OSA patients sometimes convert to central sleep apnea once established on continuous positive airway pressure (CPAP) treatment. This likely reflects a central component of unstable ventilatory control underpinning their OSA, which is then unmasked by CPAP. This phenomenon is more prevalent in patients with heart failure and pulmonary oedema where chronic hyperventilation and more unstable ventilatory control promote frequent central apneas during sleep [13]. Additionally, heart failure patients with reduced ejection fraction have been shown to shift from OSA to CSA over the course of a single night, possibly as a consequence of progressive hypocapnia and a lengthening of circulation time. Therefore, CSA and CSR may often represent a marker of underlying untreated heart failure, which may deserve consequent clinical management.

In their review article, Sanchez et al. provide an update of therapeutic interventions for patients with CSA. However, a clear practical guide on how to diagnose and how to decide on the optimal treatment strategy is not yet provided. Management of sleep disordered breathing in patients with AF requires a comprehensive

pathway approach preferably delivered by an interdisciplinary collaboration between e.g. electrophysiologists, cardiologists, and sleep specialists, as well as nurses and allied professionals, tailored to the patient's situation and preferably organized in an integrated care approach [12]. The presence of CSA/CSR should always trigger a comprehensive cardiological investigation to exclude heart failure in AF patients. If CSA/CSR remains present, even after management of heart failure and rhythm control, it is unclear which CSA requires management in AF patients [13]. Adaptive servo ventilation (ASV), which is considered to be the most effective strategy to suppress predominant CSA/CSR. 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 (SERVEHF)" trial, which recruited patients with symptomatic heart failure (NYHA class II–IV), left ventricular ejection fraction <45%, and predominant CSA/CSR. 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). Besides ASV, other CSA treatment strategies such as transvenous phrenic nerve stimulation may be considered. Although these technologies have been proven to effectively reduce CSA/CSR episodes, large randomized controlled studies investigating the effect of CSA/CSR treatment on AF outcomes are not available. Interestingly, smaller studies provide proof of concept that treatment of CSA/CSR with ASV leads to reduction in AF burden without an increase in ventricular arrhythmogenic events, an observation which needs to be confirmed in larger patient populations [14].

To conclude, AF patients typically present with predominant OSA and OSA management is recommended by current AF guidelines. In case of predominant CSA/CSR, a comprehensive work-up should be initiated to exclude heart failure and other clinical or sub-clinical comorbidities. Whether CSA/CSR, which remains even after management of heart failure and concomitant comorbidities, deserves consequent treatment in AF patients with the goal of rhythm control requires further study [15].

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

References

- [1] D. Linz, R.D. McEvoy, M.R. Cowie, V.K. Somers, S. Nattel, P. Lévy, J.M. Kalman, P. Sanders, Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: A review, *JAMA Cardiol.* 3 (6) (2018) 532–540.
- [2] S. Sousa, P. Silva Cunha, M.M. Oliveira, M. Drummond, A. Bugalho, Sleep apnea and atrial fibrillation – A different kind of rhythm, *Int. J. Cardiol. Heart Vasc.* 10 (29) (2020) 100548.
- [3] G.M. Traaen, B. Øverland, L. Aakerøy, T.E. Hunt, C. Bendz, L. Sande, S. Aakhus, H. Zaré, S. Steinshamn, O.G. Anfinnsen, J.P. Loennechen, L. Gullestad, H. Akre, Prevalence, risk factors, and type of sleep apnea in patients with paroxysmal atrial fibrillation, *Int. J. Cardiol. Heart Vasc.* 19 (26) (2019) 100447.
- [4] K. Kadhim, D.H. Lau, P. Sanders, D. Linz, Sleep apnea in atrial fibrillation – Highly prevalent, highly relevant, but most patients are not somnolent!, *Int. J. Cardiol. Heart Vasc.* 6 (26) (2020) 100463.
- [5] A. Shukla, A. Aizer, D. Holmes, et al, Effect of obstructive sleep apnea treatment on atrial fibrillation recurrence: A meta-analysis, *J. Am. Coll. Cardiol.: Clin. Electrophysiol.* 1 (2015) 41–51.
- [6] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, G. Boriani, M. Castellà, G.A. Dan, P.E. Dilaveris, L. Fauchier, G. Filippatos, J.M.

- Kalman, M. La Meir, D.A. Lane, J.P. Lebeau, M. Lettino, G.Y.H. Lip, F.J. Pinto, G.N. Thomas, M. Valgimigli, I.C. Van Gelder, B.P. Van Putte, C.L. Watkins, ESC Scientific Document Group, 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS), *Eur. Heart J.* (2020) ehaa612, <https://doi.org/10.1093/eurheartj/ehaa612>.
- [7] A.M. Sanchez, R. Germany, M.R. Lozier, M.D. Schweitzer, S. Kousseifi, R. Anand, Central sleep apnea and atrial fibrillation: A review on pathophysiological mechanisms and therapeutic implications, *Int. J. Cardiol. Heart Vasc.* 30 (2020) 100527.
- [8] D. Linz, B. Linz, M. Hohl, M. Böhm, Atrial arrhythmogenesis in obstructive sleep apnea: Therapeutic implications, *Sleep Med. Rev.* 26 (2016) 87–94.
- [9] D. Linz, U. Schotten, H.R. Neuberger, M. Böhm, K. Wirth, Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation, *Heart Rhythm.* 8 (9) (2011) 1436–1443.
- [10] D. Linz, F. Mahfoud, B. Linz, M. Hohl, S.H. Schirmer, K.J. Wirth, M. Böhm, Effect of obstructive respiratory events on blood pressure and renal perfusion in a pig model for sleep apnea, *Am. J. Hypertens.* 27 (10) (2014) 1293–1300.
- [11] D. Linz, M. Baumert, L. Desteghe, K. Kadhim, K. Vernooij, J.M. Kalman, D. Dobrev, M. Arzt, M. Sastry, H.J.G.M. Crijns, U. Schotten, M.R. Cowie, R.D. McEvoy, H. Heidbuchel, J. Hendriks, P. Sanders, D.H. Lau, Nightly sleep apnea severity in patients with atrial fibrillation: Potential applications of long-term sleep apnea monitoring, *Int. J. Cardiol. Heart Vasc.* 18 (24) (2019) 100424.
- [12] L. Desteghe, J.M.L. Hendriks, R.D. McEvoy, C.L. Chai-Coetzer, P. Dendale, P. Sanders, H. Heidbuchel, D. Linz, The why, when and how to test for obstructive sleep apnea in patients with atrial fibrillation, *Clin. Res. Cardiol.* 107 (8) (2018) 617–631.
- [13] D. Linz, M. Baumert, P. Catchside, J. Floras, P. Sanders, P. Lévy, M.R. Cowie, M. R. Doug, Assessment and interpretation of sleep disordered breathing severity in cardiology: Clinical implications and perspectives, *Int. J. Cardiol.* 15 (271) (2018) 281–288.
- [14] J.P. Piccini, S.D. Pokorney, K.J. Anstrom, O. Oldenburg, N.M. Punjabi, M. Fiuzat, G. Tasissa, D.J. Whellan, J. Lindenfeld, A. Benjafield, H. Woehrle, A. Blase, C.M. O'Connor, Adaptive servo-ventilation reduces atrial fibrillation burden in patients with heart failure and sleep apnea, *Heart Rhythm.* 16 (1) (2019) 91–97.
- [15] D. Linz, E. Ammirati, G.A. Dan, J. Heijman, D. Dobrev, Highlights from the International Journal of Cardiology Heart & Vasculature: Heart failure, atrial fibrillation, coronary artery disease and myocardial infarction, *Int. J. Cardiol. Heart Vasc.* 20 (25) (2019) 100443.

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