International Journal of Cardiology 278 (2019) 144–146

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

CPAP initiation in persistent atrial fibrillation: Have we overslept the alarm clock?

Dominik Linz [a,*], Jonathan M. Kalman [b], R. Doug McEvoy [c], Prashanthan Sanders [a]

[a] Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute (SAHMRI), University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia
[b] Department of Cardiology, Royal Melbourne Hospital, Department of Medicine, University of Melbourne, Melbourne, Australia
[c] Adelaide Institute for Sleep Health (AISH), College of Medicine and Public Health, Flinders University and Sleep Health Service, Respiratory and Sleep Services, Southern Adelaide Local Health Network, Adelaide, Australia

ARTICLE INFO

Article history:
Received 10 December 2018
Accepted 11 December 2018
Available online 13 December 2018

The results of multiple basic science and mechanistic clinical studies form a solid basis for a plausible pathophysiological link between obstructive sleep apnea (OSA) and atrial fibrillation (AF) [1]. In a meta-analysis of seven prospective cohort studies comprising 1087 patients, treatment of OSA by continuous positive airway pressure (CPAP) was associated with 40% reduction of AF recurrence after electrical cardioversion (ECV) or catheter ablation [2]. However, randomized controlled studies are lacking and this uncertainty is reflected by current international AF-guidelines, which recommend that it may be "reasonable" to perform CPAP treatment to reduce recurrent AF and optimize AF treatment results [1].

In the current issue of the International Journal of Cardiology, Caples et al. present the results of the first randomized controlled trial assessing the impact of OSA treatment on recurrence of persistent AF after ECV [3]. They screened 1757 individuals and identified 25 eligible AF patients with OSA, which were randomized to CPAP therapy or usual care. Despite reasonable adherence to CPAP therapy, CPAP could not reduce AF recurrence after ECV, which occurred in 25% of patients in the CPAP and the control group within one year.

Why did this first randomized controlled trial fail to confirm the promising antiarrhythmic effects of CPAP treatment described in previous observational studies? [2] First, the number of randomized patients was much smaller than planned in the a priori statistical analysis plan. Thus, the study is likely underpowered to detect smaller antiarrhythmic CPAP effects. Second, the inclusion criterium of an apnea-hypopnea index (AHI) >5/h is very low and resulted in a wide range in baseline AHI (13.1–71.7 in the control group and 10.0–60.8 in the CPAP group) potentially contributing to a high variability in CPAP-related antiarrhythmic effects [4]. AF recurrence during follow-up was assessed by 12-lead electrocardiograms only, which may have missed some self-terminating asymptomatic paroxysmal AF episodes. Effects on other AF treatments during follow-up (medication change, etc.) were not reported, CPAP adherence was not objectively assessed and it remains unclear, how OSA was managed when patients were not CPAP compliant.

One important difference compared to many previous observational studies is the exclusion of patients with self-reported daytime sleepiness. In the general population, treatment of OSA is classically initiated to reduce neuro-behavioural impact of OSA such as daytime sleepiness. However, a lot of AF patients do not report excessive daytime sleepiness, irrespective of the severity of OSA, possibly because the burden of symptoms due to AF may often obscure and confuse those of OSA [5]. In these AF patients without daytime sleepiness, the main goal of OSA management is to ameliorate the adverse effects of OSA on the atrium and to prevent the progression of AF, particularly in patients were rhythm control is the primary goal. Interestingly, in recent randomized controlled trials of CPAP in patients with OSA and hypertension, CPAP reduced blood pressure most effective in OSA patients with daytime sleepiness [6]. The absence of antiarrhythmic effects of CPAP treatment in persistent AF patients without daytime sleepiness suggests, that the same may also account for the effects of CPAP in patients with AF and concomitant OSA.

We also have to consider the possibility, that observational studies have largely overestimated the real antiarrhythmic effect of CPAP treatment in patients with AF. Long-term OSA has been demonstrated to result in a progressive structural remodeling process in the atrium which can maintain persistent AF episodes [7] and acute apnea associated electrophysiological changes [1] create a dynamic substrate transiently increasing the risk for shorter AF episodes [8]. While prevention of obstructive respiratory events by CPAP may reduce triggers for AF and directly translate in reduced susceptibility for new paroxysms of AF, the effect of OSA treatment on the preexisting structural atrial arrhythmogenic substrate for persistent AF episodes is more difficult to predict. OSA treatment may prevent further progression of OSA-related substrates. However, OSA is just one risk factor amongst many. Even if

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.11.100.
* Corresponding author at: Centre for Heart Rhythm Disorders, Department of Cardiology, Royal Adelaide Hospital, Adelaide 5000, Australia.
E-mail address: Dominik.Linz@adelaide.edu.au (D. Linz).

https://doi.org/10.1016/j.ijcard.2018.12.035

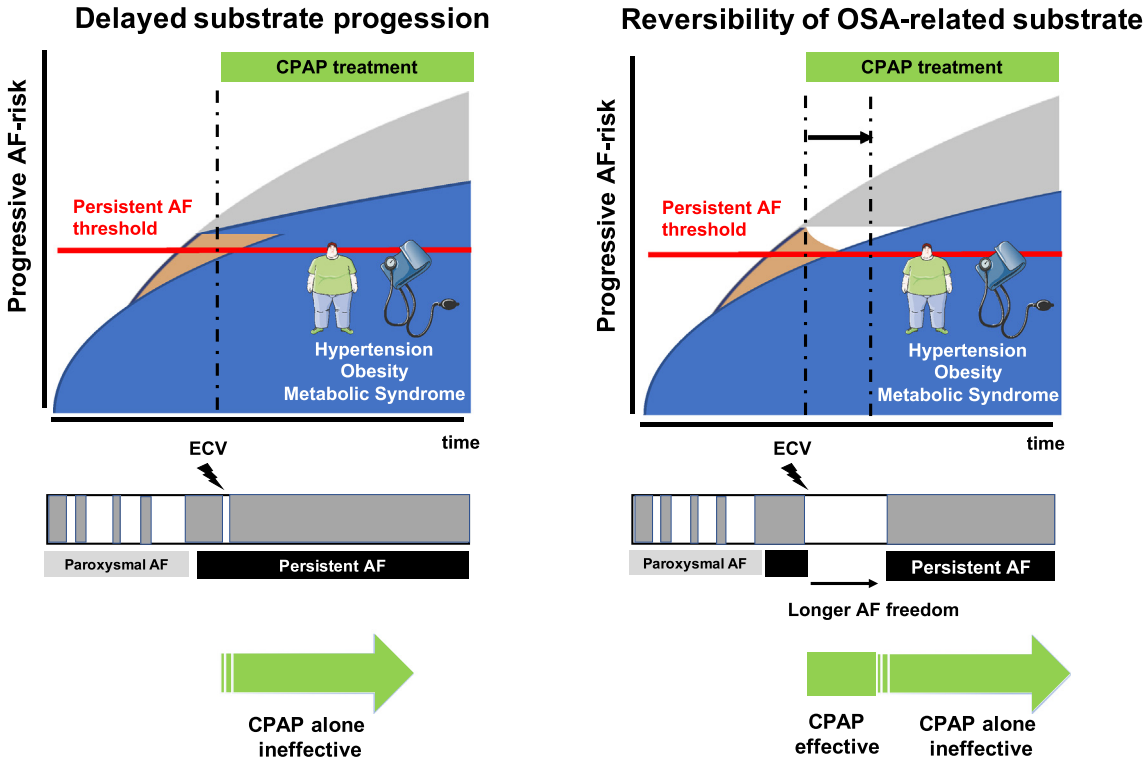

Fig. 1. Effect of continuous positive airway pressure (CPAP) on recurrence of persistent atrial fibrillation (AF) after electrical cardioversion (ECV). The progression of obstructive sleep apnea (OSA) related substrate (orange) and hypertension, obesity and metabolic syndrome related substrate (blue) are shown. Two possible scenarios: Delayed substrate progression (left panel) vs. Reversibility of OSA-related substrate (right panel).

OSA is treated, this formation of proarrhythmic substrate is further promoted by inadequately treated or unrecognized other concomitant modifiable risk factors involving hypertension, obesity and metabolic syndrome. Therefore, prevention of further progression of OSA-related AF substrates, particularly in patients with persistent AF from the outset, can in the best case maintain AF risk on the same high level but will unlikely results in a reduction of AF recurrence after ECV (Fig. 1, left panel). However, longer AF-free periods after ECV could occur if OSA-related AF substrates would be reversible during CPAP treatment (Fig. 1, right panel). Whether CPAP treatment can reverse the atrial arrhythmogenic substrate once it has been established is unknown. Given the progressive natural time-course from paroxysmal to persistent AF, persistent AF likely represents the clinical manifestation of a more progressed AF substrate. While early structural changes are mainly characterized by reactive interstitial fibrosis, long-term remodeling is characterized by scar formation and increases in atrial dimensions, which may be less or not reversible, even when the initial stressor is removed [1]. A follow-up of 12 months may be not long enough to achieve structural changes which result in a reduction of AF recurrence.

The study by Caples et al. suggests, that treatment of OSA alone without targeting concomitant risk factors cannot prevent recurrence of persistent AF after ECV. These findings therefore do not support routine CPAP treatment of OSA in patients with progressed persistent AF to maintain sinus rhythm. Importantly, an aggressive risk factor modification protocol, which included CPAP treatment of severe OSA as one important component, was able to reverses the type and natural progression of AF [9]. Therefore, early initiation of CPAP treatment in patients with paroxysmal AF, a much longer treatment period and a combination with treatment of concomitant risk factors within a multidisciplinary integrated care approach [10] might be necessary to sufficiently reverse the atrial damage to the extend in which it can influence arrhythmia recurrence in persistent AF patients. Larger multicenter prospective randomized controlled trials are currently recruiting patients to further investigate the impact of CPAP on AF burden and AF substrate reversibility in patients with OSA (SLEEP-AF trial; Trial-ID: ACTRN12616000088448 and ACTRN12616000262404).

Conflict of 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 (2018) 532–540.
[2] A. Shukla, A. Aizer, D. Holmes, S. Fowler, D.S. Park, S. Bernstein, N. Bernstein, L. Chinitz, Effect of obstructive sleep apnea treatment on atrial fibrillation recurrence: a meta-analysis, JACC Clin. Electrophysiol. 1 (2015) 41–51.
[3] S.M. Caples, M.P. Mansukhani, P.A. Friedman, V.K. Somers, The impact of continuous positive airway pressure treatment on the recurrence of atrial fibrillation post cardioversion: a randomized controlled trial, Int. J. Cardiol. 278 (2019) 133–136.
[4] D. Linz, M. Baumert, P. Catcheside, J. Floras, P. Sanders, P. Lévy, M.R. Cowie, McEvoy R. Doug, Assessment and interpretation of sleep disordered breathing severity in cardiology: clinical implications and perspectives, Int. J. Cardiol. 271 (2018) 281–288.
[5] F.N. Albuquerque, A.D. Calvin, F.H. Sert Kuniyoshi, T. Konecny, F. Lopez-Jimenez, G.S. Pressman, T. Kara, P. Friedman, N. Ammash, V.K. Somers, S.M. Caples, Sleep-disordered breathing and excessive daytime sleepiness in patients with atrial fibrillation, Chest 141 (2012) 967–973.
[6] F. Barbé, J. Durán-Cantolla, M. Sánchez-de-la-Torre, M. Martínez-Alonso, C. Carmona, A. Barceló, E. Chiner, J.F. Masa, M. Gonzalez, J.M. Marín, F. Garcia-Rio, J. Diaz de Atauri, J. Terán, M. Mayos, M. de la Peña, C. Monasterio, F. del Campo, J.M. Montserrat, Spanish Sleep And Breathing Network, Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial, JAMA 307 (2012) 2161–2168.
[7] H. Dimitri, M. Ng, A.G. Brooks, P. Kuklik, M.K. Stiles, D.H. Lau, N. Antic, A. Thornton, D.A. Saint, D. McEvoy, R. Antic, J.M. Kalman, P. Sanders, Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation, Heart Rhythm. 9 (2012) 321–327.
[8] D. Linz, A.G. Brooks, A.D. Elliott, J.M. Kalman, R.D. McEvoy, D.H. Lau, P. Sanders, Nightly variation in sleep apnea severity as atrial fibrillation risk, J. Am. Coll. Cardiol. 72 (2018) 2406–2407.

[9] M.E. Middeldorp, R.K. Pathak, M. Meredith, A.B. Mehta, A.D. Elliott, R. Mahajan, D. Twomey, C. Gallagher, J.M.L. Hendriks, D. Linz, R.D. McEvoy, W.P. Abhayaratna, J.M. Kalman, D.H. Lau, P. Sanders, PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study, Europace 20 (2018) 1929–1935.

[10] 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 (2018) 617–631.