EDITORIAL

Sleep Science

New Challenges for Sleep Apnea Research: Simple Diagnostic Tools, Biomarkers, New Treatments and Precision Medicine

Luciano F. Drager [1]*

[1] Hypertension Units from Heart Institute (InCor) and Renal Division, University of Sao Paulo Medical School, Brazil.

Corresponding author: Luciano F. Drager. Hypertension Unit – Heart Institute (InCor), University of Sao Paulo Medical School. Avenida Dr Eneas Carvalho de Aguiar, 44, CEP 05403-900 Sao Paulo, Brazil. E-mail: luciano.drager@incor.usp.br
Received: March 23, 2017; Accepted: March 24, 2017.

DOI: 10.5935/1984-0063.20170009

In the last decades, we witnessed an extraordinary development in the sleep apnea field characterized by multidisciplinary approaches that allowed us to get significant progress in our understanding of sleep apnea burden, pathophysiology consequences and developing effective treatments[1]. We rapidly learned that one of the main sleep apnea forms – namely Obstructive sleep apnea (OSA) is very common in the general population[2] and especially in patients with cardiovascular diseases[3]. Similarly, central sleep apnea (CSA) is a frequent sleep disorder observed in patients with decompensate heart failure[4]. Far beyond being common clinical conditions, evidence derived from experimental, translational and clinical observational studies consistently showed that OSA is associated with multiple consequences including increased cardiovascular risk[5-8] and that CSA is associated with worst prognosis in patients with heart failure[9].

However, all this "euphoria" came across to several challenges and realities: 1) we are not able to provide a massive strategy to improve sleep apnea underdiagnosis considering the availability of sleep laboratories and current long waitlists[10,11]; 2) the main treatment for sleep apnea (namely continuous positive airway pressure, CPAP) is not systematically available in some Countries and has significant challenges to reach long-term good adherence; 3) we observed considering variability on sleep-related symptoms and cardiovascular endpoints improvements even in those patients with good adherence to sleep apnea treatment[12]; 4) we lack effective alternative treatments, especially for severe forms of sleep apnea. In parallel to these issues, there was is growing interest to explore effective screening questionaires[13] and to expand OSA diagnosis using portable monitors and other potential tools to effectively identify OSA at very low cost[14,15].

Moreover, there is a recent interest in exploring biomarkers for sleep apnea. Much more interesting than non specific biomarkers such as C-reactive protein, recent approach using metabolomics, proteomics, microRNAs techniques (among others) gained attention to potentially identify sleep apnea signatures, biomarkers of risk[16-18] and to predict response to OSA treatment[12]. In contrast to the "wake-up call" for sleep apnea, we have recent learned that that mild OSA seems to be not associated with significant neurocognitive and cardiovascular impairment[19]. In addition, the recent neutral effects of CPAP on asymptomatic or minimally symptomatic high risk OSA patients[20,21] contribute to the recent statement from the US Preventive Services Task Force (USPSTF) to determine insufficient evidence to assess the balance of benefits and harms of screening for OSA in asymptomatic adults[22]. The recent potential harmful effects of Adaptive Servo Ventilation (ASV) for CSA in patients with heart failure[23] made us to reflect if CSA is a compensatory mechanism of heart failure or other factors such as low compliance, high dropouts and specific algorithm machines contribute to these results[24].

Therefore, the superb progress on sleep apnea field was accompanied by more questions and challenges to address in future investigations. Particular interest included

(but not limited) to advancements in new diagnostic strategies (who? how? where?), developments of useful biomarkers of risk (and not merely urine and blood exams to screening OSA), selection of patients who will most have benefit from treatment (Precision Medicine)[25] and alternative effective treatments for OSA and CSA. By the way, all these challenging research agenda are quite not surprisingly, considering the complexity of sleep…

REFERENCES

1. Lim DC, Pack AI. Obstructive Sleep Apnea: Update and Future. Annu Rev Med. 2017;68:99-112.
2. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441-6.
3. Costa LE, Uchôa CH, Harmon RR, Bortolotto LA, Lorenzi-Filho G, Drager LF. Potential underdiagnosis of obstructive sleep apnoea in the cardiology outpatient setting. Heart. 2015;101(16):1288-92.
4. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160(4):1101-6.
5. Drager LF, Polotsky VY, O'Donnell CP, Cravo SL, Lorenzi-Filho G, Machado BH. Translational approaches to understanding metabolic dysfunction and cardiovascular consequences of obstructive sleep apnea. Am J Physiol Heart Circ Physiol. 2015;309(7):H1101-11.
6. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046-53.
7. Lee CH, Sethi R, Li R, Ho HH, Hein T, Jim MH, et al. Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. Circulation. 2016;133(21):2008-17.
8. Uchôa CH, Danzi-Soares Nde J, Nunes FS, de Souza AA, Nerbass FB, Pedrosa RP, et al. Impact of OSA on cardiovascular events after coronary artery bypass surgery. Chest. 2015;147(5):1352-60.
9. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, et al. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation. 1999;99(11):1435-40.
10. Rotenberg B, George C, Sullivan K, Wong E. Wait times for sleep apnea care in Ontario: a multidisciplinary assessment. Can Respir J. 2010;17(4):170-4.
11. Flemons WW, Douglas NJ, Kuna ST, Rodenstein DO, Wheatley J. Access to diagnosis and treatment of patients with suspected sleep apnea. Am J Respir Crit Care Med. 2004;169(6):668-72.
12. Sánchez-de-la-Torre M, Khalyfa A, Sánchez-de-la-Torre A, Martinez-Alonso M, Martinez-García MÁ, Barceló A, et al.; Spanish Sleep Network. Precision Medicine in Patients With Resistant Hypertension and Obstructive Sleep Apnea: Blood Pressure Response to Continuous Positive Airway Pressure Treatment. J Am Coll Cardiol. 2015;66(9):1023-32.
13. Marti-Soler H, Hirotsu C, Marques-Vidal P, Vollenweider P, Waeber G, Preisig M, et al. The NoSAS score for screening of sleep-disordered breathing: a derivation and validation study. Lancet Respir Med. 2016;4(9):742-8.
14. Chai-Coetzer CL, Antic NA, Hamilton GS, McArdle N, Wong K, Yee BJ, et al. Physician Decision Making and Clinical Outcomes With Laboratory Polysomnography or Limited-Channel Sleep Studies for Obstructive Sleep Apnea: A Randomized Trial. Ann Intern Med. 2017;166(5):332-40.
15. Nakano H, Hirayama K, Sadamitsu Y, Toshimitsu A, Fujita H, Shin S, et al. Monitoring sound to quantify snoring and sleep apnea severity using a smartphone: proof of concept. J Clin Sleep Med. 2014;10(1):73-8.
16. Xu H, Zheng X, Qian Y, Guan J, Yi H, Zou J, et al. Metabolomics Profiling for Obstructive Sleep Apnea and Simple Snorers. Sci Rep. 2016;6:30958.
17. Seetho IW, Ramírez-Torres A, Albalat A, Mullen W, Mischak H, Parker RJ, et al. Urinary proteomic profiling in severe obesity and obstructive sleep apnoea with CPAP treatment. Sleep Sci. 2015;8(2):58-67.
18. Tan HL, Kheirandish-Gozal L, Gozal D. The promise of translational and personalised approaches for paediatric obstructive sleep apnoea: an 'Omics' perspective. Thorax. 2014;69(5):474-80.
19. Chowdhuri S, Quan SF, Almeida F, Ayappa I, Batool-Anwar S, Budhiraja R, et al.; ATS Ad Hoc Committee on Mild Obstructive Sleep Apnea. An Official American Thoracic Society Research Statement: Impact of Mild Obstructive Sleep Apnea in Adults. Am J Respir Crit Care Med. 2016;193(9):e37-54.
20. Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunström E. Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial. Am J Respir Crit Care Med. 2016;194(5):613-20.
21. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al.; SAVE Investigators and Coordinators. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med. 2016;375(10):919-31.
22. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, et al. Screening for Obstructive Sleep Apnea in Adults: US Preventive Services Task Force Recommendation Statement. JAMA;2017;317(4):407-114.
23. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015;373(12):1095-105.
24. Naughton MT, Kee K. Sleep apnoea in heart failure: To treat or not to treat? Respirology. 2017;22(2):217-229.
25. McEvoy RD, Michael MZ. Measuring Blood microRNAs to Provide Personalized Advice to Sleep Apnea Patients With Resistant Hypertension: Dreaming the Future. J Am Coll Cardiol. 2015;66(9):1033-5.