Thoracic aortic aneurysms: expanding the potential cardiovascular consequences of obstructive sleep apnoea

Luciano F. Drager[1,2] and Miguel A. Martinez-Garcia[3,4]

Affiliations: [1]Hypertension Unit, Heart Institute (InCor), University of São Paulo, São Paulo, Brazil. [2]Hypertension Unit, Renal Division, University of São Paulo, São Paulo, Brazil. [3]Pneumology Dept, Hospital Universitario i Politécnico La Fe, Valencia, Spain. [4]Centro de Investigación Biomédica en Red (CIBERES), Instituto de Salud Carlos III, Madrid, Spain.

Correspondence: Luciano F. Drager, Hypertension Unit, Heart Institute (InCor), University of Sao Paulo Medical School, Avenida Dr Eneas de Carvalho Aguiar, 44, CEP 05403-900 Sao Paulo, Brazil.
E-mail: luciano.drager@incor.usp.br

@ERSpublications
This editorial highlights recent evidence suggesting that a common sleep-related breathing disorder, namely obstructive sleep apnoea, may contribute to thoracic aneurism expansion independent from traditional risk factors https://bit.ly/38nxKBY

Cite this article as: Drager LF, Martinez-Garcia MA. Thoracic aortic aneurysms: expanding the potential cardiovascular consequences of obstructive sleep apnoea. *Eur Respir J* 2021; 57: 2004440 [https://doi.org/10.1183/13993003.04440-2020].

Over the course of the past decades, we have observed an increased interest in exploring the complex relationships between cardiovascular diseases and obstructive sleep apnoea (OSA) [1]. However, the vast majority of studies have focused their attention on coronary and cerebrovascular diseases and cardiac arrhythmias, without considering other important cardiovascular diseases, such as pulmonary embolism or aortic disorders.

Thoracic aortic aneurysm (TAA) is an indolent but dangerous disease characterised by the progressive confined dilation of the thoracic aorta layers [2]. As many as 21% of patients who suffer from acute aortic events (including dissection and rupture) die before receiving medical attention [3, 4]. In the USA, TAAs are considered the 18th most common cause of death in individuals aged more than 55 years, being the primary cause of 9923 deaths in 2018 [5].

The traditional risk factors for TAA include ageing, high blood pressure, tobacco use, atherosclerosis, bicuspid aortic valve, family history (20% exhibit an autosomal dominant pattern of inheritance resulting from a single gene mutation), and presence of some genetic conditions leading to medial degeneration, such as Marfan, Loeys–Dietz and Ehler–Danlos syndromes [6–8]. Despite significant advancements in this research area, it is conceivable that other modifiable factors may influence the growth rate of TAAs. This statement is supported by the fact that a proportion of TAAs continues to expand regardless of good blood pressure control, aggressive strategies for lipid-lowering and smoking cessation.

In the current issue of the *European Respiratory Journal*, Gaisl *et al.* [9] shed light upon the potential role of OSA on the progression of TAAs (predefined as an aortic diameter exceeding the sex-specific cut-offs at the level of the sinus of Valsalva: ⩾39 mm for women, ⩾44 mm for men; or the ascending aorta: ⩾42 mm for women, ⩾46 mm for men). The authors followed 230 patients with yearly standardised echocardiographic measurements of the ascending aorta over 3 years and two level-III sleep studies to detect OSA (defined by an apnoea–hypopnoea index (AHI) ⩾15 events per h). None of the patients had a

Received: 7 Dec 2020 | Accepted: 25 Dec 2020

syndromic connective tissue disorder (*e.g.* Marfan, Ehlers–Danlos or Loeys–Dietz syndromes), or a major vascular inflammatory disorder (*e.g.* Takayasu/giant cell arteritis). The primary outcome was the continuous analysis of TAA expansion rate in relation to the AHI value. Secondary outcomes included surveillance for aortic events (composite end-points of rupture, dissection, elective surgery and death). At baseline, there was no association between TAA diameter and AHI. After 3 years, mean expansion rates were 0.55±1.25 mm at the aortic sinus and 0.60±1.12 mm at the ascending aorta. In the regression analysis, after controlling for baseline diameter and cardiovascular risk factors, there was strong evidence for a positive association of TAA expansion with AHI (aortic sinus estimate 0.025 mm, 95% CI 0.009–0.040; ascending aorta estimate 0.026 mm, 95% CI 0.011–0.041). TAA expansion rates were larger in higher AHI categories. With regard to alternative markers of OSA severity, oxygen desaturation index was consistent with the main AHI results, suggesting that intermittent hypoxia may also play a role in this scenario. In the secondary analysis, 20 participants (8%) experienced an aortic event; however, there was no association with OSA severity.

The potential reasons by which OSA is probably a "new kid on the block" in the TAA research area are multiple. Several hypotheses have been discussed, including the impact of intermittent hypoxia, oxidative stress and intrathoracic pressure changes leading to shear stress on the artery walls. The sympathetic overactivity associated with OSA may also play a role, contributing to increased blood pressure variability [10]. In addition, OSA has been associated with increased aortic stiffening, especially in those with hypertension [11]. A recent investigation suggests that measures of aortic stiffness and pulsatile haemodynamics are independently associated with future TAA growth [12]. Although the role of blood pressure dipping pattern on TAA expansion is unclear, we cannot discard the potential impact of attenuated and "riser" blood pressure patterns frequently associated with OSA [13].

We congratulate the authors for paving the way for research into the impact of OSA on aortic diseases. The same group had previous contributions on the association of OSA with aortic disease in Marfan's syndrome [14, 15] and, more importantly, with abdominal aneurysm expansion in patients with severe OSA [16]. The current prospective investigation has a notable sample size (considering the overall prevalence of TAA), underscoring the importance of sleep researchers' interaction with investigators from tertiary cardiology services. Despite the several strengths, the cohort studied by Gaisl *et al.* [9] has significant considerations and limitations to note. First, it is important to contextualise the real impact of OSA on TAAs. Aortic diameter at baseline is by far the main factor of variability. In their model, >80% of the variability in the follow-up measurements of the aortic sinus and the ascending aorta were explainable by the baseline diameter value alone. Considering the sub-millimetre confidence interval for AHI in the current study, the proposed clinical impact of OSA severity on TAA expansion remained relatively small during the 3-year period of this study. Therefore, it is appropriate to say that OSA may represent one of the few potentially modifiable risk factors underlying TAAs but its contribution is modest. Second, since TAA is a lifelong disease, the 3-year follow-up is too short, thus limiting our comprehension of the real burden of OSA on TAAs. For instance, no patient experienced a TAA rupture and/or emergency surgery for TAA. Third, although validated, the use of transthoracic echocardiogram to evaluate TAAs expansion provides substantially less information than computed tomography angiogram or magnetic resonance angiography. Ultrasound technology examinations did not allow the inclusion of TAA analysis at the level of the descending aorta [17]. On the other hand, such technologies based on tomography or magnetic resonance techniques are expensive and can eventually be associated with risks including radiation exposure and nephrotoxicity from contrast agents. In this scenario, transthoracic echocardiogram is helpful for surveillance programmes of TAA [17]. Another important issue is that indirect mechanisms by which OSA contributes to TAA (including blood pressure variability and non-dipping blood pressure) were not explored. Ideally, it would be interesting to have 24-h blood pressure monitoring data to explore these "indirect" effects on TAA.

In conclusion, we are expanding our current knowledge about the potential role of OSA in the evolution of patients with aortic aneurysms. The available literature and the current paper suggest that OSA is currently serving as a potential "second hint" in patients with aortic diseases. Whether OSA is, *per se*, a risk factor for developing TAA, or whether OSA treatment may mitigate TAA expansion (and therefore decrease the rate of surgical procedures and severe complications, such as aortic rupture) deserves future investigation. Indeed, preliminary data in 71 patients that experienced an acute aortic dissection found that the false lumen dilatation was related to the severity of OSA [18]. Finally, we share the opinion that a closer look should be given to the complications of large vessels in OSA, in order to expand our comprehension about the cardiovascular consequences of this important sleep-related breathing disorder.

Conflict of interest: L.F. Drager has nothing to disclose. M.A. Martinez-Garcia has nothing to disclose.

References

1 Drager LF, McEvoy RD, Barbe F, *et al.* Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation* 2017; 136: 1840–1850.
2 Saeyeldin AA, Velasquez CA, Mahmood SUB, *et al.* Thoracic aortic aneurysm: unlocking the silent killer secrets. *Gen Thorac Cardiovasc Surg* 2019; 67: 1–11.
3 Olsson C, Thelin S, Ståhle E, *et al.* Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation* 2006; 114: 2611–2618.
4 Mészáros I, Mórocz J, Szlávi J, *et al.* Epidemiology and clinicopathology of aortic dissection. *Chest* 2000; 117: 1271–1278.
5 National Center for Injury Prevention and Control. WISQARS Leading Causes of Death Reports, 1999–2018. https://webappa.cdc.gov/sasweb/ncipc/leadcause.html Date last accessed: 30 November 2020. Date last updated: 20 February 2020.
6 Yiu RS, Cheng SW. Natural history and risk factors for rupture of thoracic aortic arch aneurysms. *J Vasc Surg* 2016; 63: 1189–1194.
7 Harky A, Fan KS, Fan KH. The genetics and biomechanics of thoracic aortic diseases. *Vasc Biol* 2019; 1: R13–R25.
8 Pinard A, Jones GT, Milewicz DM. Genetics of thoracic and abdominal aortic diseases. *Circ Res* 2019; 124: 588–606.
9 Gaisl T, Rejmer P, Roeder M, *et al.* Obstructive sleep apnoea and the progression of thoracic aortic aneurysm: a prospective cohort study. *Eur Respir J* 2021; 57: 2003322.
10 Gaisl T, Bratton DJ, Kohler M. The impact of obstructive sleep apnoea on the aorta. *Eur Respir J* 2015; 46: 532–544.
11 Drager LF, Bortolotto LA, Figueiredo AC, *et al.* Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. *Chest* 2007; 131: 1379–1386.
12 Boczar KE, Boodhwani M, Beauchesne L, *et al.* Aortic stiffness, central blood pressure, and pulsatile arterial load predict future thoracic aortic aneurysm expansion. *Hypertension* 2021; 77: 126–134.
13 Genta-Pereira DC, Furlan SF, Omote DQ, *et al.* Nondipping blood pressure patterns predict obstructive sleep apnea in patients undergoing ambulatory blood pressure monitoring. *Hypertension* 2018; 72: 979–985.
14 Kohler M, Blair E, Risby P, *et al.* The prevalence of obstructive sleep apnoea and its association with aortic dilatation in Marfan's syndrome. *Thorax* 2009; 64: 162–166.
15 Kohler M, Pitcher A, Blair E, *et al.* The impact of obstructive sleep apnea on aortic disease in Marfan's syndrome. *Respiration* 2013; 86: 39–44.
16 Mason RH, Ruegg G, Perkins J, *et al.* Obstructive sleep apnea in patients with abdominal aortic aneurysms: highly prevalent and associated with aneurysm expansion. *Am J Respir Crit Care Med* 2011; 183: 668–674.
17 Nienaber CA, Kische S, Skriabina V, *et al.* Noninvasive imaging approaches to evaluate the patient with known or suspected aortic disease. *Circ Cardiovasc Imaging* 2009; 2: 499–506.
18 Delsart P, Juthier F, Clough RE, *et al.* Prognostic significance of sleep apnea syndrome on false lumen aortic expansion in post-acute aortic syndrome. *Ann Thorac Surg* 2016; 102: 1558–1564.