Adverse Thoracic Aortic Remodeling in Obstructive Sleep Apnea

Mahesh K. Vidula[1] and Julio A. Chirinos[1,2]

Obstructive sleep apnea (OSA) is associated with various cardiovascular conditions, including hypertension, arrhythmias, coronary artery disease, and pulmonary hypertension.[1] Multiple mechanisms for these associations have been proposed, including intermittent hypoxia, changes in intrathoracic pressure, activation of the sympathetic nervous system, and inflammation.[2,3] The presence of negative intrathoracic pressure during apneic episodes also favors an increased pressure difference across the aortic wall, which may contribute to thoracic aortic remodeling and enlargement.[4] The association between OSA and thoracic aortic size has been evaluated in prior studies, but these analyses have been limited by small sample sizes, and the relationship remains unclear.[5]

In this issue of the *American Journal of Hypertension*, Gherbesi *et al.*[5] conducted a systematic review and meta-analysis to comprehensively assess whether OSA is indeed associated with thoracic aortic dilatation. The authors identified 11 studies which in total included 1,862 patients diagnosed with OSA and without connective tissue diseases or known aortic pathology. Most of these studies utilized echocardiography (n = 8), followed by computed tomography (n = 2) and magnetic resonance imaging (n = 1), to measure thoracic aortic diameter. Of these 11 studies, 5 studies compared aortic root and ascending aorta diameters in patients with and without OSA, and a meta-analysis of these 5 studies revealed larger aortic diameters in the OSA group when compared with the control group (standard means difference: 0.73 ± 0.08 mm, confidence interval: 0.57–0.88, $P < 0.0001$). In these studies, the authors found that systolic blood pressure had a modest positive correlation with aortic diameter ($r = 0.29$, $P < 0.001$). Four studies compared aortic sizes across differing severities of OSA, and a meta-analysis of these studies found increased aortic diameters in severe OSA group as opposed to mild OSA (standard means difference: 0.42 ± 0.07 mm, confidence interval: 0.28–0.56, $P < 0.0001$). Participants in the severe OSA group were also noted to have higher body mass index than the participants in the mild OSA group.

The study by Gherbesi *et al.* adds useful information to the body of literature regarding the association of OSA with thoracic aortic size and remodeling. The study design overcomes the limitation of the small sample sizes of previously performed individual studies. These findings provide additional evidence suggesting a relationship between OSA and thoracic aortic remodeling, while also raising the possibility of increased aortic dilatation with worsening severity of OSA. However, the magnitude of differences in aortic diameter found in both of these sets of analyses was small.

In addition to its strengths, some important limitations of the study must also be noted. First, the confounding effect of obesity should be considered, since OSA is strongly associated with obesity. Indeed, several of the cardiovascular abnormalities present in obese adults with OSA appear to result predominantly from obesity, rather than OSA per se[6]; alternatively, cardiovascular consequences of OSA may be modified by the presence of obesity.[7] In addition, it is well known that aortic size and aortic hemodynamic function are associated with body size.[8,9] Given that obesity increases body size, it is essential to account for the normal allometric relationships between body size and aortic diameter, when attempting to discern the effect of OSA on the aorta. While the optimal method for achieving normalization of aortic diameter for body size remains unclear, available data indicate that indexing by body surface area (BSA) or height can help improve the risk stratification of patients with enlarged aortic diameters.[10] However, it is important to note that ratiometric (i.e., linear) indexation for these parameters of body size, as is often recommended, does not fully account for the underlying relationship between aortic size and body size. Indeed, the allometric exponent for the relationship between BSA and aortic root diameter has been shown to be sublinear (~0.6, rather than 1),[11] implying that aortic diameter should be normalized for BSA raised to the power of 0.6. Unfortunately, most studies included in this meta-analysis did not index the aortic diameters by body size or only performed ratiometric indexation. Therefore, the authors could not assess how obesity, or more generally, body size would influence their findings. Future studies studying the relationship between

Correspondence: Julio A. Chirinos (julio.chirinos@pennmedicine.upenn.edu).

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[1]Division of Cardiovascular Medicine, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA.

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aortic size and OSA should apply adequate methods for allometric normalization of aortic size and should carefully explore the confounding or modifying effects of obesity.

An additional point of consideration is whether the relationship between OSA and aortic size detected in this analysis is mediated by other prevalent factors known to be associated with aortic dilatation. For instance, OSA is associated with hypertension, which is a well-known risk factor for aortic remodeling. In this meta-analysis, the authors found that aortic diameter and systolic blood pressure were significantly correlated, suggesting that the higher aortic diameters in the OSA group may be at least partially due to hypertension. Furthermore, it is well established that aortic size increases with age,[8,10] but the potential effect of age differences between participants with OSA and controls was not addressed in this meta-analysis. Future studies should assess the independent association between aortic size and OSA, while accounting for factors known to be associated with aortic dilatation.

Gherbesi *et al*. provide a timely contribution to our understanding of the relationship between OSA and aortic size. Their meta-analysis suggests an association of OSA and aortic size, and further generates the possibility of increased aortic sizes with worsening severity of OSA. Future studies are warranted to assess the degree to which this association is independent of body size, age, and various comorbidities and to assess the mechanisms and clinical consequences of aortic remodeling in individuals with OSA.

DISCLOSURE

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REFERENCES

1. Cowie MR, Linz D, Redline S, Somers VK, Simonds AK. Sleep disordered breathing and cardiovascular disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2021; 78:608–624.
2. Lu M, Wang Z, Zhan X, Wei Y. Obstructive sleep apnea increases the risk of cardiovascular damage: a systematic review and meta-analysis of imaging studies. *Syst Rev* 2021; 10:212.
3. Bauters F, Rietzschel ER, Hertegonne KB, Chirinos JA. The link between obstructive sleep apnea and cardiovascular disease. *Curr Atheroscler Rep* 2016; 18:1.
4. Gaisl T, Bratton DJ, Kohler M. The impact of obstructive sleep apnoea on the aorta. *Eur Respir J* 2015; 46:532–544.
5. Elisa Gherbesi MT, Andrea F, Carla S, Stefano C, Cesare C. Sleep apnea syndrome and large artery subclinical damage: targeting thoracic aorta dilatation. *Am J Hypertens* 2022; 35:543–550.
6. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, Foster GD, Maislin G, Saif H, Broderick P, Chittams J, Hanlon AL, Pack AI. CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014; 370:2265–2275.
7. Xu L, Keenan BT, Maislin D, Gislason T, Benediktsdóttir B, Gudmundsdóttir S, Gardarsdottir M, Staley B, Pack FM, Guo X, Feng Y, Chahwala J, Manaktala P, Hussein A, Reddy-Koppula M, Hashmath Z, Lee J, Townsend RR, Schwab RJ, Pack AI, Kuna ST, Chirinos JA. Effect of obstructive sleep apnea and positive airway pressure therapy on cardiac remodeling as assessed by cardiac biomarker and magnetic resonance imaging in nonobese and obese adults. *Hypertension* 2021; 77:980–992.
8. Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos C, Rocchi G, Sicari R, Nihoyannopoulos P, Zamorano J, Pepi M, Breithardt OA, Plonska-Gosciniak E; European Association of Echocardiography. Echocardiography in aortic diseases: EAE recommendations for clinical practice. *Eur J Echocardiogr* 2010; 11:645–658.
9. Chirinos JA, Rietzschel ER, De Buyzere ML, De Bacquer D, Gillebert TC, Gupta AK, Segers P; Asklepios investigators. Arterial load and ventricular-arterial coupling: physiologic relations with body size and effect of obesity. *Hypertension* 2009; 54:558–566.
10. Goldstein SA, Evangelista A, Abbara S, Arai A, Asch FM, Badano LP, Bolen MA, Connolly HM, Cuéllar-Calàbria H, Czerny M, Devereux RB, Erbel RA, Fattori R, Isselbacher EM, Lindsay JM, McCulloch M, Michelena HI, Nienaber CA, Oh JK, Pepi M, Taylor AJ, Weinsaft JW, Zamorano JL, Dietz H, Eagle K, Elefteriades J, Jondeau G, Rousseau H, Schepens M. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging: endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2015; 28:119–182.
11. Oxborough D, Ghani S, Harkness A, Lloyd G, Moody W, Ring L, Sandoval J, Senior R, Sheikh N, Stout M, Utomi V, Willis J, Zaidi A, Steeds R. Impact of methodology and the use of allometric scaling on the echocardiographic assessment of the aortic root and arch: a study by the Research and Audit Sub-Committee of the British Society of Echocardiography. *Echo Res Pract* 2014; 1:1–9.