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COMMENTARY

Is CPAP preventing the long-term progression of arterial stiffness in patients with obstructive sleep apnea?

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Obstructive sleep apnea (OSA) is a neglected condition in which repetitive upper airway obstructions occurs during sleep and exposes the cardiovascular system to intermittent hypoxia, arousals and abrupt reductions in the negative intrathoracic pressure.[1] In the last two decades, consistent evidence from the literature suggests that OSA is a systemic disease with major cardiovascular consequences. Data from the Sleep Heart Healthy Study showed that severe OSA is independently associated with all-cause mortality due to coronary artery disease, particularly in men aged 40–70 years.[2] In addition, a Spanish observational study showed that treatment of OSA with continuous positive airway pressure (CPAP) was associated with a significant decrease in nonfatal (myocardial infarction, stroke, coronary artery bypass surgery and percutaneous transluminal coronary angiography) and fatal (death from myocardial infarction or stroke) cardiovascular events.[3] Therefore, it is conceivable that OSA contributes to vascular remodeling and atherosclerosis progression.[4]

Arterial stiffness is increasingly recognized as a surrogate end point for cardiovascular disease and is considered a useful tool for assessment of subclinical target organ damage.[5] Arterial stiffness is associated with presence of cardiovascular risk factors, atherosclerotic disease and, more importantly, is a strong predictor of future cardiovascular events and all-cause mortality.[6] Recently, several investigators have explored the effects of OSA on arterial stiffness. Compared to control groups, higher levels of arterial stiffness (measured mainly by carotid-femoral pulse wave velocity) have been consistently observed in OSA patients with and without comorbidities.[7–10] More importantly, OSA treatment with CPAP for relatively short periods of time (ranging from 1 to 4 months) significantly decrease pulse wave velocity.[11,12] In one study, pulse wave velocity decrease after CPAP treatment occurred in association with improvements in sympathetic and inflammatory markers.[11] Despite these encouraging findings, the long-term effects of OSA treatment on atherosclerosis are not available.

In this issue, Saito *et al.*[13] provide data that extend the current knowledge in this important research area. The authors studied 212 male OSA patients (114 hypertensives and 98 normotensives) submitted to a long-term (2 years) CPAP therapy. Anthropometric, blood pressure and brachial-ankle pulse wave velocity were measured at baseline and after 6, 12 and 24 months of CPAP treatment. The authors found that in both hypertensive and normotensive patients, pulse wave velocity decreased in the first 6 months of treatment, before increasing gradually from 6 to 24 months. In parallel, body weight, heart rate, systolic and diastolic blood pressure decreased significantly in the hypertensive group over the 2 years of CPAP treatment. Multivariate regression analysis revealed that age, decrease in diastolic blood pressure, heart rate, and higher initial levels of serum high-density lipoprotein-cholesterol were independent factors related to changes in pulse wave velocity over the 2 years of CPAP treatment in all patients.

Overall, the major contribution of the study of Saito *et al.*[13] was to provide data about the long-term effects of OSA treatment on arterial stiffness. OSA treatment with CPAP clearly decreased pulse wave velocity in the first 6 months, being this effect more evident in the hypertensive group. These results suggest that CPAP treatment may prevent the long-term progression of arterial stiffening especially in OSA patients with comorbidities. The regression analysis also pointed that weight lost and improvements in the hemodynamic profile may be important contributors to decrease arterial stiffness in these patients. Another interesting finding is that patients with OSA were on average minimally symptomatic regarding daytime sleepiness (determined by the Epworth Sleepiness Scale). Recent evidence showed a small fall in blood pressure that may not be clinically significant in non-sleepy patients.[14] These results raises questions about the necessity of treating patients with OSA and no complains of excessive daytime sleepiness. However, the present results showed that CPAP is effective in minimally symptomatic patients and are in line with other studies that have shown that OSA is associated with endothelial dysfunction and markers of atherosclerosis irrespective of daytime symptoms.[10,15]

The findings of Saito *et al.*[13] are subject to limitations, the majority of them were clearly addressed by the authors. Because this was a nonrandomized study, there are no data from a control group (that is, no treatment or Sham CPAP therapy). Therefore, the present investigation does not allow definitive conclusions on the long-term effects of OSA

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treatment on arterial stiffness progression. The authors observed that even under treatment, patients with OSA presented a gradual increase in the pulse wave velocity over the 18 months of the study (although these increase did not exceed the baseline values). Because OSA *per se* increases arterial stiffness,[7–12] especially in moderate to severe forms of OSA, it is reasonable to speculate that the progression of vascular remodeling and atherosclerosis is more pronounced in patients with OSA than in the general population. This important point should be addressed in future investigations. Second, there is no detailed information regarding CPAP adherence overtime. Therefore, it is unknown if CPAP adherence was an independent predictor of pulse wave velocity evolution. Finally, the authors did not fully control the main results for adherence of antihypertensive medications. Changes in medications over time could influence cardiovascular parameters including arterial stiffness and should be taken into account as elegantly shown by Barbe *et al.*[14]

In conclusion, the study of Saito *et al.*[13] provides evidence that CPAP therapy in patients with OSA significantly decreases arterial stiffness in the first 6 months and may also prevent the long-term increase of arterial stiffening for longer periods of time. It is highly desirable to determine whether a reduction in markers of vascular remodeling and atherosclerosis such as arterial stiffness is a therapeutic goal in terms of hard clinical end points such as cardiovascular morbidity and mortality in patients with OSA.

1 Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences. *Lancet* 2009; **373**: 82–93.
2 Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM. Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009; **6**: e1000132.
3 Marin JM, Carrizo SJ, Vicente E, Augusti 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**: 1046–1053.
4 Lorenzi-Filho G, Drager LF. Obstructive sleep apnea and atherosclerosis: a new paradigm. *Am J Respir Crit Care Med* 2007; **175**: 1219–1221.
5 Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H, European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; **27**: 2588–2605.
6 Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; **55**: 1318–1327.
7 Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005; **172**: 613–618.
8 Drager LF, Bortolotto LA, Figueiredo AC, Silva BC, Krieger EM, Lorenzi-Filho G. Obstructive sleep apnea, hypertension, and their interaction on arterial stiffness and heart remodeling. *Chest* 2007; **131**: 1379–1386.
9 Tsioufis C, Thomopoulos K, Dimitriadis K, Amfilochiou A, Tousoulis D, Alchanatis M, Stefanadis C, Kallikazaros I. The incremental effect of obstructive sleep apnoea syndrome on arterial stiffness in newly diagnosed essential hypertensive subjects. *J Hypertens* 2007; **25**: 141–146.
10 Drager LF, Bortolotto LA, Maki-Nunes C, Trombetta IC, Alves MJ, Fraga RF, Negrão CE, Krieger EM, Lorenzi-Filho G. The incremental role of obstructive sleep apnoea on markers of atherosclerosis in patients with metabolic syndrome. *Atherosclerosis* 2010; **208**: 490–495.
11 Drager LF, Bortolotto LA, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea. *Am J Respir Crit Care Med* 2007; **176**: 706–712.
12 Kohler M, Pepperell JC, Casadei B, Craig S, Crosthwaite N, Stradling JR, Davies RJ. CPAP and measures of cardiovascular risk in males with OSAS. *Eur Respir J* 2008; **32**: 1488–1496.
13 Saito T, Saito T, Sugiyama S, Asai K, Yasutake M, Mizuno K. Effects of long-term treatment for obstructive sleep apnea on pulse wave velocity. *Hypertens Res* 2010; **33**: 844–849.
14 Barbé F, Durán-Cantolla J, Capote F, de la Peña M, Chiner E, Masa JF, Gonzalez M, Marín JM, Garcia-Rio F, de Atauri JD, Terán J, Mayos M, Monasterio C, del Campo F, Gomez S, de la Torre MS, Martinez M, Montserrat JM, Spanish Sleep and Breathing Group. Long-term effect of continuous positive airway pressure in hypertensive patients with sleep apnea. *Am J Respir Crit Care Med* 2010; **181**: 718–726.
15 Kohler M, Craig S, Nicoll D, Leeson P, Davies RJ, Stradling JR. Endothelial function and arterial stiffness in minimally symptomatic obstructive sleep apnea. *Am J Respir Crit Care Med* 2008; **178**: 984–988.