Is obstructive sleep apnoea an innocent bystander in the pathophysiology of arterial stiffening?

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Arterial compliance is an important mechanical property of the arterial tree that is crucial for the maintenance of vascular homeostasis and cardiovascular health. There are a number of factors that variably decrease arterial compliance and therefore increase arterial stiffness in different arterial segments. For example, arteries become less distensible and therefore stiffer as blood pressure (BP) increases, and this effect occurs throughout the arterial tree. On the other hand, an increase in the collagen–elastin ratio in the arterial wall, such as occurs with ageing, increases arterial stiffness predominantly in large elastic arteries like the aorta. In contrast, an increase in the quantity and tone of arterial smooth muscle mainly increases arterial stiffness in the smaller conduit arteries such as the femoral arteries.[1 2]

Overall, a loss of arterial compliance gives rise to increased arterial stiffness and poorer maintenance of vascular homeostasis, and this is likely to be a key driver of cardiovascular disease (CVD). The process of arterial stiffening occurs in ageing populations and in conditions that are strongly associated with CVD including chronic kidney disease,[3] type II diabetes and various components of the metabolic syndrome.[4] This has led to the development of many methods for quantifying arterial stiffness,[5] as a means of improving CVD risk stratification in populations with comorbid disease. However, in order to standardise the assessment of risk, the American Heart Association Council for high blood pressure research recommends the non-invasive measurement of the carotid-femoral pulse wave velocity as the preferred method.[6] Studies have established that an increase in pulse wave velocity (PWV) of 1 m/s increases CVD events by 14% and CVD mortality by 15%.[7]

Obstructive sleep apnoea (OSA) has in recent years been increasingly linked with an increased prevalence and incidence of CVD independent of traditional risk factors including age and obesity.[8] In this context, numerous studies have demonstrated an association between OSA and increased arterial stiffness[5] with some studies explicitly demonstrating additional (independent) effects beyond classical risk factors that promote arterial stiffening, such as the metabolic syndrome.[9] Furthermore, several observational studies have shown a reduction in a range of arterial stiffness measurements following treatment of OSA with nasal CPAP.[5] However, the majority of studies have only included small numbers, and most were of short duration. In addition, most were uncontrolled observational studies. Among the few randomised controlled trials (RCT), some[10–12] but not all,[13 14] demonstrated reductions in measures of arterial stiffness with CPAP. This lack of a consistent effect with CPAP may be due to a number of factors including small sample sizes, variability in patient characteristics including presence versus absence of comorbid risk factors, elevated versus normal baseline BP and arterial stiffness, variability in CPAP compliance and length of CPAP treatment and variability in the methods of arterial stiffness assessment. Nevertheless, the lack of OSA treatment does not appear to reduce the effectiveness of antihypertensive treatment in reducing 24 hour BP and PWV in hypertensive patients, suggesting that it is not a major driver of arterial stiffness.[15] Therefore, it still remains unclear whether OSA can be truly implicated as a causal factor for increased arterial stiffness or whether it is in fact an innocent bystander. Given the high prevalence in OSA of comorbid conditions that are well proven to promote arterial stiffening including obesity, hypertension, dyslipidaemia, glucose intolerance and type II diabetes, it is important that further studies involving larger samples of patients are conducted to address the 'uncertainty of causality'.

In an effort to address this, Joyeux-Faure *et al*[16] report on the results of a meta-analysis to explore whether and to what extent OSA 'drives' arterial stiffness. They used individual data from 893 patients (72% men, mean age 56±11 years) who participated in nine statistically homogeneous studies conducted between 2006 and 2015 at their institution. Six of the nine studies included analysis of baseline data from randomised trials. All subjects were well characterised in terms of anthropometric variables (age, body mass index, gender) and other comorbidities (BP, antihypertensive use, diabetic and lipid lowering medications). OSA was assessed either by full polysomnography or respiratory polygraphy and confirmed in 84% of patients. All patients underwent carotid-femoral PWV assessment using a standardised protocol with the same Complior (Alam Medical, France) device. The sample included a wide spectrum of OSA and obesity severities as well as a moderate to high prevalence of hypertension (78%), type 2 diabetes (45%) and dyslipidaemia (62%) which are known drivers for increased arterial stiffness. PWV varied widely among patients (5.3 m/s to 20.5 m/s) with a mean (±SD) value of 10.4±2.3 m/s. This contrasts with an expected mean PWV (±2 SD) of 8.3 m/s (4.5–12.1) in similarly aged people who have normal BP and no additional cardiovascular risk factors.[17]

As expected, the initial univariate analysis found that increased PWV was strongly associated with the traditional risk factors of age, BP, diabetes and dyslipidaemia. However, neither OSA-related hypoxia nor severe OSA (defined by an Apnoea Hypopnea Index (AHI) ≥30 events/hour) was associated with increased PWV. Interestingly, subjective sleepiness defined by an Epworth Sleepiness Scale (ESS) score ≥9 (which was highest in patients with severe OSA) was associated with a reduced PWV, suggesting that sleepiness may have confounded the effects in patients with severe OSA. However, ultimately in the final multivariable analysis, only age, systolic BP and type 2 diabetes remained significantly associated with increased PWV.

The authors acknowledged several limitations of their analysis. Heterogeneity might have been introduced with the mixed use of polygraphy and polysomnography across studies and by including studies with different eligibility criteria. Use of polygraphy could dilute the difference in PWV attributable to severe OSA due to the increased probability of diluting OSA severity in

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many patients secondary to poor sleep on the night. There was also significant hypoxia in the control (non-OSA) group due to COPD or morbid obesity which may have also diluted the OSA effect. In addition to these acknowledged limitations, it is important to recognise that all patients were recruited on the basis of suspected OSA, most (72%) were men, all were from a single centre, and it was unclear whether the population was predominantly of the same ethnicity. These factors could all make the findings non-generalisable. In this sense, collaborative databank sharing comprising individual data from international studies that used similar PWV techniques would be more appropriate to prevent this limitation. Furthermore, the study contained only 58 patients (~6%) without OSA (AHI <5) which effectively limits the analysis almost entirely to an OSA population in which CVD risk factors are notoriously common, and this clinical referral bias could increase the likelihood of a null finding. In this context, all OSA-related variables were analysed as dichotomous variables using cut points instead of continuous variables, and this approach may have reduced the power to detect true associations.

Regardless of the aforementioned potential limitations, the analysis should be recognised for its valuable contribution to the evidence base which to date has been limited for the reasons previously stated. There was adequate power to rigorously explore the independent association between OSA and increased arterial stiffness measured in a standardised way using the gold standard carotid-femoral PWV. Whether OSA contributes to arterial stiffness in the more muscular conduit arteries was not able to be determined, and hopefully future adequately powered analyses will be able to explore this. Finally, it is important to highlight that while the analysis did aim to explore the extent to which OSA 'drives' arterial stiffness, causality cannot be inferred from this cross-sectional data. Further analyses of data from randomised trials are needed. In this context, it would be interesting to see whether individual patient data from the RCT studies included in this analysis would shed light on a causal association.

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