Obstructive sleep apnoea and cardiovascular calcification

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The increased cardiovascular risk associated with obstructive sleep apnoea (OSA) has been well established,[1] but the mechanisms involved remain to be elucidated. The study by Lutsey *et al*,[2] published in this issue of *Thorax* adds another piece to the puzzle of the link between OSA and cardiovascular risk by showing significant associations between parameters of sleep-disordered breathing and coronary atherosclerotic calcification.

The initiation and progression of atherosclerosis is characterised by an accumulation of lipids and lipoproteins within the vascular wall, leading to immune activation and the recruitment of inflammatory cells.[3] The resulting atherosclerotic plaques may remain silent for a long time before plaque destabilisation occurs, leading to plaque rupture, vessel occlusion and, if in a coronary artery, myocardial infarction. Prognostic markers are of particular interest to identify patients at risk of plaque rupture and who would benefit from preventive actions and medical treatments. In this context, OSA may represent an important modifiable cardiovascular risk factor.

In addition to lipid accumulation and inflammation, vascular calcification plays an important role in atherosclerosis. Although initially considered purely degenerative, atherosclerotic calcification is in fact an active process, which involves calcium deposits, procalcifying particles and a phenotypic transdifferentiation of vascular smooth muscle cells towards an osteoblastic phenotype. Recently, special attention has been paid to the pattern of punctate vascular calcification, since such microcalcifications may be a site of plaque destabilisation and drive plaque rupture.

Scoring the amount of calcium in the coronary arteries by means of CT provides a non-invasive measure of the total atherosclerosis burden. Increased coronary artery calcification (CAC) has been associated with increased cardiovascular risk and shown to provide further prognostic information in addition to traditional cardiovascular risk factors. Evidence is now accumulating linking sleep disturbances with increased CAC,[2 4 5] and inflammation may represent an important factor when it comes to OSA-induced atherosclerotic calcification.

The association of increased sleep fragmentation and low sleep quality with increased CAC[2 5] implicates sympathetic nervous activation, which in turn may activate inflammatory circuits. However, it is, above all, the typical breathing pattern in OSA causing an intermittent hypoxia, which is a potent proinflammatory stimulus.[1] Among the inflammatory mediators explored as putative links between OSA and increased cardiovascular risk can be mentioned, for example, lipid mediators of inflammation, such as leukotrienes.[6] Subjects with OSA exhibit an increased leukotriene production,[7] and signalling through leukotriene receptors increases experimental atherosclerosis.[8] Moreover, leukotriene signalling has also been associated with cardiovascular calcification,[9] which in the context of the results of Lutsey *et al*[2] opens up for further exploration of leukotrienes and other inflammatory mediators in OSA-induced atherosclerotic calcification. Interestingly, the use of the leukotriene receptor antagonist montelukast in asthma has, in addition, been associated with a decreased cardiovascular risk,[10] further reinforcing the therapeutic implications of this pathway. This point is of particular clinical relevance since 6 months of treatment with CPAP, which is the reference treatment of OSA, does not reduce the plasma levels of either CRP or several proinflammatory mediators in patients with severe OSA.[11 12]

Although significant associations between OSA and CAC are reported in this issue of *Thorax*,[2] it should be taken into consideration that only severe OSA remained significantly correlated with CAC after adjustment for traditional cardiovascular risk factors. Likewise, a previous study found significant associations with CAC only in non-obese OSA subjects.[4] This illustrates the complexity of the interaction between sleep-disordered breathing and atherosclerotic calcification, and the multifactorial participation of the increased cardiovascular risk associated with OSA.

Taken together, although the mechanisms linking OSA to cardiovascular calcification remain to be established, the observed association of OSA with CAC[2] reinforces the proatherogenic effects of sleep-disordered breathing and intermittent hypoxia. Nevertheless, multiple comorbidities of patients with OSA must be taken into consideration when studying OSA-associated cardiovascular risk and calcification. The challenges for the future perspectives in this domain lie in the identification of patients with OSA at particular risk of plaque rupture and in the development of specific preventive strategies targeting the pathways of cardiovascular calcification induced by OSA and intermittent hypoxia.

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