The effect of obstructive sleep apnea syndrome and snoring severity to intima-media thickening of carotid artery

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Data from epidemiological studies and randomized clinical trials strongly suggest that obstructive sleep apnea (OSA) is associated with elevated risk of cardiovascular events [1]. Although OSA and cardiovascular diseases share many risk factors, studies have demonstrated that OSA is an independent risk factor of arterial hypertension and atherosclerosis [2]. The mechanisms of this relationship are incompletely understood. However, the evidence suggests that intermittent hypoxia and the arousal response are likely the main pathophysiologic factors associated with oscillation of systemic and pulmonary arterial blood pressures, heart rate, and cardiac function. These factors expose the heart and circulation to a cascade of noxious stimuli that, over time, may initiate or contribute to the progression of most cardiovascular disorders.

In everyday practice, attention is usually paid to atherosclerotic plaques in the vessels, typical of advanced atherosclerosis with organ dysfunction. However, atherosclerosis is a chronic, progressive, pathological process with a long asymptomatic subclinical phase. Therefore, assessment of the early stages of atherosclerotic changes, such as intima-media thickness (IMT) measurement, seems to be a much better approach. Ultrasonography—a noninvasive, quick, and reproducible technique—can be used to evaluate the atherosclerotic process at an early stage. Carotid IMT correlates well with anatomic measurements and is a marker of both structural vascular damages and in prediction of the cardiovascular risk in asymptomatic healthy subjects [3].

Epidemiological and interventional studies frequently use Carotid IMT as a surrogate marker for subclinical or early atherosclerosis. In order to evaluate the possible effect of OSA on the subclinical carotid atherosclerosis, in this issue of sleep and breathing, Dr Salepci and colleagues examined the association between the severity of OSA and the snoring with carotid artery IMT. In this study, ultrasonography of carotid artery was performed in three groups of subjects: the habitual snoring group ($n=14$), the mild–moderate OSAS ($n=53$), and the severe OSA groups ($n=35$). They found that carotid IMT was significantly higher in severe compared to mild–moderate group. Furthermore, carotid artery IMT was highly correlated with OSA and snoring severity and this relation had age as independent determinant. However, they didn't find statistically significant difference of IMT between OSA and snoring group, probably, as the authors explain, due to the small number of patients in the snoring group, and the subjects in three groups investigated were not fully matched with regard to variables known to influence carotid artery IMT, such as age and BMI.

In the literature, several studies have assessed the association between snoring and OSA severity with subclinical atherosclerosis, using carotid artery IMT in different OSA populations [4]. Despite the differences in selection of the patients and control groups, the majority of studies have found that carotid IMT is increased in OSA patients compared to controls independent of other factors and that overall thickness of the intima-media increases with severity of sleep apnea. Comparison of the results of the current study of Dr Salepci with those of previous studies is troublesome as they vary with respect to selection of participants and methodology. Most of the studies, as this one, were based on typical populations of patients with OSA, i.e., they had numerous comorbidities, they didn't have a control group and duration of symptoms was not taken into account. Another important consideration is that existing data is limited by the lack of prospective studies that would

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establish a causal relationship between subclinical atherosclerosis with OSA. For a better understanding of the relationships between OSA and vascular complications, monitoring of the inflammatory process seems to be necessary, e.g., CRP, which levels are correlated with AHI, mean and lowest SaO₂ and arousal index independently of age, BMI, waist, and neck circumference [5]. Therefore, assessing markers of systemic inflammation such as CRP in conjunction with noninvasive measurement of subclinical CVD would help elucidate the role of systemic inflammation in the association between OSA and subclinical atherosclerosis, and need to be clarified in future studies.

Although the authors showed the relationship between snoring and OSA with thickening of intima-media thickness, they were not sufficient to prove that OSA itself is responsible for the development of early atheromatous changes. Numerous risk factors, such as anthropometric parameters, smoking, hyperlipidemia, and hypertension, might affect this relationship. Moreover, the influence of physical activity and alcohol intake on IMT was not studied. The authors recognise that common cardiovascular risk factors could represent confounding variables in their results; however, the inclusion of patients with hypertension, hyperlipidemia, and smoking history represents a major limitation of their study. Indeed, recruitment of patients with OSA and without comorbidities is a difficult task as this group of patients is not representative of the usual population of patients with OSAS encountered in clinical practice who exhibit a high burden of cardiovascular risk factors. Nevertheless, there are few studies [6–8] showing increased IMT in patients suffering from OSA alone. Taking this into account, an independent influence of OSA on atherosclerotic changes of the arterial wall is strongly suggested, representing further that OSA may be a risk factor on its own for the emergence of cardiovascular disease.

What are the clinical implications of the above findings? As early atherosclerosis exists in patients with snoring and OSA, even without cardiovascular comorbidities, we should not overlook the atherosclerotic risks of these patients. The question, therefore, that arises, is whether individuals with OSA should be screened for subclinical cardiovascular disease (CVD), or whether certain subpopulations, such as patients severe disease, would demonstrate greater benefit from screening for subclinical CVD. In order to answer this question, prospective data is required to assess which patients would benefit most from more aggressive therapeutic approaches for CVD prevention, allowing us to intervene to halt the progression of the disease and decrease the vascular risk of these patients. Moreover, the development of a strategy for early detection of subclinical CVD might be an additional

indication for treating patients with OSA with CPAP, given that the severity of OSA is independently associated with worsening subclinical atherosclerosis. There is increasing evidence that the effects of OSA on the cardiovascular system are reversible with treatment. In a recent prospective study [9], CPAP treatment resulted in a significant reduction in carotid artery IMT compared to those who opted for conservative treatment over a study period of 1 year. Therefore, as the authors of this study explain, patients newly diagnosed with OSA should be encouraged to comply with CPAP not just to relieve daytime sleepiness but also for the cardio-protective effects. Lastly, the presence of a significant association between OSA and subclinical CVD should make us consider whether OSA warrants being included as one of the risk factors in the algorithms for determination of future risk of CVD events.

In conclusion, subclinical atherosclerosis, for which carotid artery IMT has been considered as an early marker, has been well studied in patients with OSA. However, it is still unclear how OSA per se contributes to the increased risk of these events and how much may be due to confounding factors. Further studies are needed to identify OSA patients prone to develop vascular changes which would benefit most from more aggressive treatment. Nevertheless, health care providers should be encouraged to screen patients for snoring and OSA in order to start, in certain subpopulations, regular assessment and follow up of early detection of carotid pathology in conjunction with patient education about vascular risk factors and appropriate lifestyle changes.

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