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EDITORIAL

The vascular micromilieu in obstructive sleep apnoea

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Obstructive sleep apnoea (OSA) is increasingly recognised as an important cardiovascular risk factor. In particular, OSA has been shown to increase the risk of diurnal arterial hypertension in a dose-dependent manner, and is now considered as one of the most common causes of secondary arterial hypertension [1, 2]. Furthermore, OSA increases the likelihood of developing vaso-occlusive disease, notably myocardial infarction and stroke, although this association seems to be weaker than that observed for arterial hypertension [3]. Of note, the epidemiological studies demonstrating a genuine relationship between OSA and cardiovascular disorders have been controlled with respect to confounding factors such as age, body weight and metabolic disease.

How does one explain the causal link between OSA and cardiovascular disease? The repetitive collapse of the upper airway during sleep generates a unique pattern of hypoxia, with frequent cycles of hypoxia and re-oxygenation during the night, and a constant normoxia while awake. Accumulating evidence suggests that this chronic intermittent hypoxia causes a specific disturbance in the vascular micromilieu, with vasoconstrictive, pro-inflammatory and pro-coagulant forces predominating. Finally, the disturbance in the vascular micromilieu leads to endothelial dysfunction in these patients [4]. This reduction in endothelial-dependent vasorelaxation has been established as a pathogenic factor in both systemic arterial hypertension and atherosclerosis. Treatment of OSA by continuous positive airway pressure (CPAP) ventilation not only eliminates apnoeas and nocturnal oxygen desaturations, but also exerts cardio-protective effects. Thus, CPAP therapy has been demonstrated to ''normalise'' the vascular micromilieu, to restore endothelial function and to lower 24-h blood pressure [5, 6].

The disturbance in the vascular micromilieu in OSA is characterised by sympathetic activation, insulin resistance, increased oxidative stress and, possibly, a state of hypercoagulability. Sympathetic activation is indicated by increased plasma and urinary levels of adrenaline/noradrenaline, as well as enhanced muscle sympathetic nerve activity (as measured by peroneal nerve microneurography [7, 8]). It is believed that sympathetic over-activity is mainly responsible for the development of arterial hypertension in OSA. Furthermore, as catecholamines increase glucose levels, sympathetic activation probably leads to insulin resistance in untreated OSA patients [9]. Decreased insulin sensitivity itself may promote the emergence of arterial hypertension and atherosclerosis.

Oxidative stress is another major mechanism that may explain the increased cardiovascular morbidity and mortality observed in OSA. Direct evidence for increased oxidative stress in OSA comes from two studies reporting enhanced *in vitro* release of free oxygen radicals from isolated neutrophils and monocytes [10, 11]. These radicals may lead to a breakdown of endothelial-derived nitric oxide and to exaggerated lipid peroxidation, since both phenomena occur in OSA [12, 13]. These effects may subsequently promote blood pressure elevations and accelerated atherosclerosis in affected patients. Haemostatic alterations to the vascular micromilieu, for example enhanced platelet activation and an increase in plasma fibrinogen levels, have also been described in OSA (for review see [14]) and may provide a further explanation for the high prevalence of vascular diseases in these patients.

More recent work suggests that OSA patients also suffer from vascular inflammation. This is supported by studies that report an increase in circulating levels of endothelial adhesion molecules (*i.e.* soluble intercellular adhesion molecules and soluble vascular cell adhesion molecules [15]), cytokines (*i.e.* interleukin-1, -6 and -8 and tumour necrosis factor-α [16]), matrix metalloproteinases [17] and acute phase proteins (*i.e.* highly sensitive C-reactive protein, serum amyloid-A [18, 19]). Furthermore, *in vitro* experiments have delineated that monocytes and $\gamma\delta$-T-cells from OSA patients bind more tightly to layers of endothelial cells than those from control subjects [11, 20]. Presumably, this effect is mediated by an upregulation of adhesion molecules on the surface of these cells. In addition, the same cells are more injurious to the cultured endothelium, probably through an enhanced production and release of the above-mentioned cytokines. Taken together, these changes may significantly contribute to the development of inflammation-driven atherosclerosis. Along these lines, some groups have reported that OSA patients have a greater intima-media-thickness of their common carotid arteries when compared with matched controls [21, 22]. This parameter reflects the early stages of atherosclerosis and is viewed as an accurate predictor of overall cardiovascular risk.

The current report of DYUGOVSKAYA *et al*. [23] in this issue of the *European Respiratory Journal* contributes a novel aspect to the ever-growing complex picture of the vascular micromilieu in OSA. In this study, the cytotoxicity of CD8+ T-lymphocytes against human umbilical vein endothelial cells was investigated in three different patient groups: untreated OSA patients; control subjects; and single-night CPAP-treated OSA patients. These cells displayed increased cytotoxicity in the untreated OSA group, whereas CPAP therapy resulted in a

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lower cytotoxic potential, which was comparable to that of the control group. The authors conclude that CD8+ T-lymphocytes also participate in inflammatory/immune mechanisms in OSA and that this may equally be related to atherogenic sequelae in these patients.

One may criticise the study as the OSA patients had accompanying diseases that could also impact on lymphocyte activity (*i.e.* arterial hypertension and ischaemic heart disease). However, statistical analysis demonstrated that the OSA and control groups did not significantly differ with regard to these co-morbidities. Finally, the fact that CD8+ T-lymphocyte cytotoxicity was lower in CPAP-treated OSA patients clearly argues against the view that the observed *in vitro* effects were due to confounding factors. A further possible limitation of the study may be that the effects of short-term CPAP therapy on CD8+ T-lymphocyte cytotoxicity were assessed in a different subset of OSA patients. However, some of the initially diagnosed, untreated OSA patients were re-investigated after several months of CPAP therapy and showed similar phenotypic and functional changes in their CD8+ T-lymphocytes. Thus, there is little doubt as to the significance of the findings of DYUGOVSKAYA *et al*. [23].

What remains to be done? Future studies investigating vascular disease biomarkers and cell biology in OSA should preferably enrol otherwise healthy OSA patients and closely matched control groups. Furthermore, reversibility testing after CPAP therapy in these studies should be more refined (*i.e.* inclusion of short- and long-term observations, sham-CPAP arms and, possibly, measurements after CPAP withdrawal). Finally, changes in biomarkers and cell activity should be related to biological parameters of the cardiovascular system, for example blood pressure, intima-media-thickness or endothelial-dependent vasodilation.

Certainly, the basic mechanisms of the disturbance to the vascular micromilieu in OSA need to be further clarified. In this context, one feasible approach is to set up animal models of OSA-related cardiovascular disease, for example targeted deletion of candidate genes in experimental animals.

Regardless of these considerations, the data of DYUGOVSKAYA *et al*. [23] and others lay important groundwork for the initiation of pharmacological intervention studies to prevent and/or treat the cardiovascular complications of obstructive sleep apnoea. Such studies may, for example, test the effects of antioxidants, nitric oxide donors and anti-inflammatory agents (*i.e.* statins, *etc*.). If these drugs prove beneficial, then they may be of special value in those obstructive sleep apnoea patients who discontinue or refuse continuous positive airway pressure therapy.

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