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Continuous positive airway pressure and platelet activation in obstructive sleep apnoea.

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Obststructive sleep apnoea (OSA) is a complex condition associated with a number of cardiovascular sequelae including hypertension (both systemic and pulmonary), congestive heart failure, arrhythmias, myocardial infarction and stroke [1-6]. However, the recent American Heart Association/American College of Cardiology scientific statement on sleep apnoea suggests that there is a paucity of data for a causal role of OSA in cardiovascular disease [7] which underlines the importance of studies such as that of Akinnusi and co-workers in this edition of *Respiration* that are aimed at understanding the pathophysiology of OSA [8]. The condition is caused by multiple episodes of airway collapse during the course of sleep which causes large oscillations in intrathoracic pressure and in arterial blood gases. It is well known that chronic continuous hypoxia can cause changes in coagulation and in platelet number and function [9] and that changes in platelet function are associated with adverse cardiovascular effects [10]. Recently, it has been shown in rats that platelet activation can occur also when the hypoxia is intermittent [11]. Taken together, this provides good reason to suspect that alterations in platelet function as a consequence of the intermittent hypoxia of sleep apnoea may underlie some of the adverse cardiovascular effects associated with the condition. In support of this hypothesis, Akinnusi and co-workers demonstrate that there are elevated plasma

sCD40L levels and platelet-monocyte aggregates in sleep apnoea patients and that this is correlated with hypoxia severity and that these effects are ameliorated by continuous positive airway pressure (CPAP), a treatment that relieves the obstruction and the hypoxia [8]. Previous studies did not find any effect on platelet aggregation in sleep apnoea patients [12,13] but several other studies have reported increased platelet activation and aggregation [14-18]. More recently, similar to Akinnusi and co-workers findings, an increase in sCD40L levels in sleep apnoea patients that was decreased by CPAP has been reported in two separate studies [5,19] with both studies showing a positive correlation with hypoxia severity.

To our knowledge, platelet number was not measured in any of these studies except for that of Minoguchi and co-workers [5] in which there was no difference in number compared to obese controls. Chronic continuous hypoxia is known to cause an early thrombocytosis and a subsequent thrombocytopenia. In just one study, chronic intermittent asphyxia in rats had no effect on platelet number [11].

CD40L is a transmembrane protein and a member of the TNF family and also exists in a soluble form (sCD40L) in plasma which originates from activated platelets [20]. The interaction of CD40L with its receptor CD40 plays a major role in inflammation and increased levels of sCD40L are known to be associated with increased risk of cardiovascular events

[21,22] and is also known to play a role in the pathogenesis of atherosclerosis [23,24]. However, as the primary source of sCD40L is activated platelets, sCD40L also acts as a biomarker of platelet activation and platelet activation is itself associated with increased risk of cardiovascular disease [25,26]. Once activated, platelets secrete over 300 biologically active proteins [27], any of which may play a role in the pathogenesis of cardiovascular disease, as well as forming platelet aggregates which cause the vessel occlusion associated with myocardial infarction. The study of Akinnusi and co-workers shows an association between sCD40L and sleep apnoea but it provides no evidence of a role for sCD40L in the pathogenesis of cardiovascular disease in these patients where it may simply be a biomarker of platelet activation.

Recently CPAP has been shown to improve endothelial function [28] and to reduce blood pressure [29,30], sympathetic tone [31] and platelet activation [8,18] in patients with OSA. Thus, CPAP clearly reduces many of the risk factors for adverse cardiac events although the exact mechanism is not clear. Norman and co-workers showed that while CPAP reduced blood pressure, nocturnal continuous oxygen therapy did not, even though it raised haemoglobin oxygen saturation levels, suggesting that a mechanism other than hypoxia may be involved [29]. It is not clear from the platelet studies whether a similar situation exists. Thus, while CPAP improves sleep and reduces daytime drowsiness [32], it also improves many of the underlying risk factors for cardiovascular disease.

The work of Akinnusi et al has added to the body of evidence for a role for platelet activation in the cardiovascular disease associated with sleep apnoea and suggests that CPAP can decrease this platelet activation and therefore may improve both

quality and duration of the life of OSA patients.

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