Lung (2008) 186:195–196
DOI 10.1007/s00408-008-9090-x

EDITORIAL

Hypercoagulability: Another Potential Mechanism of Obstructive Sleep Apnea-Related Cardiovascular Disease?

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Received: 4 March 2008 / Accepted: 19 March 2008 / Published online: 22 April 2008

Obstructive sleep apnea (OSA) is a common disease with substantial health and economic impact [1–3]. During sleep, the upper airway collapses repeatedly leading to sleep fragmentation and oxyhemoglobin desaturation. Furthermore, there are compelling epidemiologic data implicating OSA in the development of myocardial infarction and cerebrovascular events. For example, Marin et al. [4] published data from a cohort of patients with varying degrees of sleep-disordered breathing (snorers, mild-severe OSA) and healthy participants who were followed for a mean of 10 years. Patients with severe untreated OSA had a much greater risk of developing fatal (odds ratio [OR] = 2.87, 95% CI = 1.17–2.51) and non-fatal cardiovascular disease (CVD) (OR = 3.17, 95% CI = 1.12–7.51) compared to healthy controls after adjustment for potential confounding factors. Patients with OSA who were treated with CPAP did not have an increased rate of events (OR = 1.05, 95% CI = 0.39–2.21 and OR = 1.42, 95% CI = 0.52–3.4, respectively) compared to healthy controls, suggesting that substantial benefits may be seen with therapy.

In another study, Peker et al. [5] prospectively followed 182 middle-aged men with no hypertension or CVD at baseline who were referred for a sleep study. Incident CVD (i.e., hypertension, coronary artery disease, stroke, myocardial infarction, arrhythmias) over 7 years occurred in 37% of patients with OSA compared to 6.6% in those without OSA. In a study from the Sleep Heart Health Cohort, the prevalence of CVD, including myocardial infarction, angina, coronary revascularization, heart failure, and stroke was 1.42 times greater in patients with OSA (apnea-hypopnea index [AHI] > 11 events/h) compared to those without OSA (AHI = 0–1.3 events/h) after controlling for potential confounders [6].

The pathophysiology of CVD secondary to OSA is complex. Patients with OSA have sustained activation of the sympathetic nervous system, systemic inflammation with increased levels of inflammatory mediators such as C reactive protein and IL-6 [7], glucose intolerance/insulin resistance [8], other metabolic derangements [9], and endothelial dysfunction [10]. Many of these physiologic/biochemical abnormalities are implicated in the pathogenesis of CVD and represent potential pathogenic mechanisms.

Another potential mechanism is blood hypercoagulability. Data from the Framingham cohort has shown that each standard deviation increment in the level of the procoagulant molecule fibrinogen was associated with a 20% increased risk of coronary heart disease for men and 30% for women. A 10% increased risk of stroke was noted in both sexes. [11]. In a meta-analysis of 18 studies by Danesh et al. [12], higher fibrinogen was associated with a relative risk of 1.8 (95% CI = 1.6–2.0) for coronary heart disease.

Patients with OSA suffer from increased hypercoagulability. Blood viscosity and hematocrit are greater in patients with OSA compared to controls [13, 14]. Patients with OSA also suffer from increased platelet activity [15, 16]. Serum levels of procoagulant molecules such as fibrinogen [17], activated clotting factor VII (FVIIa), XIIa, and thrombin/antithrombin III complexes are increased in patients with OSA [18].

Another potential contributing mechanism is decreased fibrinolytic activity, as reflected by higher levels of

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plasminogen activator inhibitor-1 (PAI-1). In a large prospective cohort study of 10,500 male participants, the odds ratio for CVD per standard deviation increase in PAI-1 was 1.38 (CI = 1.27–1.49) [19]. Kohler et al. [20] have elegantly reviewed potential mechanisms by which PAI-1 may contribute to an increased risk of CVD.

Zamarrón et al. [21] studied 96 male subjects and measured levels of PAI-1. Levels of PAI-1 were greater in patients with OSA and hypertension (105.0 ng/ml) than in the OSA-only group (57.0 ng/ml, $p < 0.001$). Both groups had higher PAI-1 levels than controls (39.7 ng/ml, $p < 0.001$). These findings are consistent with other investigators. Von Känel et al. [22] have shown that PAI-1 levels are significantly correlated with mean oxygen saturation and AHI. Similarly, Rångemark et al. [23] demonstrated greater PAI-1 levels in patients with OSA, with a trend toward higher values in those with lower minimum overnight oxygen saturation. The mechanisms leading to decreased fibrinolysis in OSA are not clear. It is possible that hypoxia and repeated increase in sympathetic nervous system activity may lead to increased production of PAI-1 [24]. In this regard, PAI-1 levels are increased in other conditions associated with oxidative stress and tissue hypoxia [25].

Although we must be cautious given the small sample size and cross-sectional nature, the study by Zamarrón et al. [21] further highlights the potential role of hypercoagulability as a possible mechanistic pathway in the development of cardiovascular complications in patients with OSA. Future prospective epidemiologic studies linking PAI-1 levels to important clinical events (such as stroke or myocardial infarction) in OSA patients and examining the impact of OSA therapy on PAI-1 levels would be useful to understanding whether impaired fibrinolysis is truly an important cardiovascular biomarker in OSA.

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