Sleep Medicine Reviews 18 (2014) 25–34

Contents lists available at SciVerse ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

Circulating adhesion molecules in obstructive sleep apnea and cardiovascular disease

Victoria M. Pak [a,b,*], Michael A. Grandner [a], Allan I. Pack [a]

[a] Center for Sleep and Circadian Neurobiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[b] Department of Biobehavioral Health Sciences, University of Pennsylvania School of Nursing, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 9 October 2012
Received in revised form
7 January 2013
Accepted 8 January 2013
Available online 22 April 2013

Keywords:
Cardiovascular diseases
Epidemiological studies
Atherosclerosis
Sleep apnea
Adhesion molecules

SUMMARY

Over 20 years of evidence indicates a strong association between obstructive sleep apnea (OSA) and cardiovascular disease. Although inflammatory processes have been heavily implicated as an important link between the two, the mechanism for this has not been conclusively established. Atherosclerosis may be one of the mechanisms linking OSA to cardiovascular morbidity. This review addresses the role of circulating adhesion molecules in patients with OSA, and how these may be part of the link between cardiovascular disease and OSA. There is evidence for the role of adhesion molecules in cardiovascular disease risk. Some studies, albeit with small sample sizes, also show higher levels of adhesion molecules in patients with OSA compared to controls. There are also studies that show that levels of adhesion molecules diminish with continuous positive airway pressure therapy. Limitations of these studies include small sample sizes, cross-sectional sampling, and inconsistent control for confounding variables known to influence adhesion molecule levels. There are potential novel therapies to reduce circulating adhesion molecules in patients with OSA to diminish cardiovascular disease. Understanding the role of cell adhesion molecules generated in OSA will help elucidate one mechanistic link to cardiovascular disease in patients with OSA.

Introduction and overview

Obstructive sleep apnea (OSA) is a leading public health problem, affecting 5–15% of adults,[1] and it is associated with repetitive episodes of transient oxygen desaturation during sleep (caused by partial or complete obstruction of the airway), resulting in cyclical, intermittent hypoxia and sleep fragmentation. There is growing evidence that OSA is an independent risk factor for cardiovascular disease,[2,3] although the pathogenesis is not completely understood. Although the mechanism for the initiation of cardiovascular disease has not been fully established, one theorized mechanism is the intermittent hypoxia produced by the frequent respiratory events.[4] The repeated episodes of hypoxia followed by re-oxygenation that occur in the context of OSA are proposed to result in oxidative stress and increased production of reactive oxygen species (ROS).[5] The formation of oxygen free radicals from intermittent hypoxia and re-oxygenation is thought to lead to activation of transcriptional factors such as nuclear factor-kappa B (NFκB) that upregulate the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1) and cytokines (such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, IL-8, and chemokines).[4,6–8] Inflammation is recognized as playing a role in all stages of the atherosclerotic disease process; for this reason, evaluation of circulating biomarkers of inflammation, including adhesion molecules, has become recognized as a useful tool for identifying patients at high risk for future cardiovascular events.[9] Since OSA is associated with elevated cardiovascular risk, and inflammation plays an important role in the development of cardiovascular disease, it is reasonable to suspect that OSA may confer risk through an inflammatory mechanism. As adhesion molecules are a key component of the inflammatory process, it is likely that, if OSA is associated with increased inflammation, OSA will also be associated with increased adhesion molecules. Further, it is possible that these elevations in adhesion molecules could be ameliorated with treatment of OSA.

Cell adhesion molecules are cell surface proteins involved in the binding of cells (usually leukocytes) to endothelial cells or to the extracellular matrix.[9] The adhesion of circulating leukocytes to the endothelial cells is believed to be one of the initial steps in the pathogenesis of atherosclerosis.[10,11] In both animal and human

* Corresponding author. Center for Sleep and Circadian Neurobiology, University of Pennsylvania, 3624 Market Street, Suite 201, Philadelphia, PA 19104, USA. Tel.: +1 215 615 4374; fax: +1 215 701 1831.
E-mail addresses: mmpak@mail.med.upenn.edu, vicpak1@yahoo.com (V.M. Pak).

1087-0792/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.smrv.2013.01.002

Abbreviations

AHI	apnea hypopnea index
BMI	body mass index
CAD	coronary artery disease
CAMS	cell adhesion molecules
CPAP	continuous positive airway pressure
CRP	C-reactive protein
ELISA	enzyme linked immunosorbent assay
EPCs	endothelial progenitor cells
FMD	flow-mediated dilation
ICAM	intercellular adhesion molecule
IL	interleukin
MCP	monocyte chemoattractant protein
NF-κB	nuclear factor-kappa B
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
PECAM	platelet endothelial cell adhesion molecule
PMN	polymorphonuclear neutrophil
PSGL	P-selectin glycoprotein ligand
ROS	reactive oxygen species
sICAM	soluble ICAM
SMC	smooth muscle cells smooth muscle cells
sVCAM	soluble VCAM
TNF	tumor necrosis factor
VCAM	vascular cell adhesion molecule

models of atherosclerosis, the adherence of monocytes and lymphocytes to the intact endothelial lining is one of the earliest detectable events in atherosclerosis.[11–13]

Adhesion molecules can be measured in the circulation. The shedding of cellular adhesion molecules from the surface of an activated endothelium via proteolytic cleavage allows for measurable plasma levels of soluble cellular adhesion molecules. Although cell-bound adhesion receptors are challenging to study *in vivo*, circulating levels of soluble VCAM-1 (sVCAM-1) have been correlated with cellular VCAM-1 expression in the human aorta from samples obtained during surgery.[14] To our knowledge, there have not been studies *in vivo* involving circulating levels of soluble ICAM-1 (sICAM-1) and correlation to cellular ICAM-1 in the human aorta. However, the assessment of soluble adhesion molecules may be useful biomarkers for stratifying disease risk and prognosis for atherosclerosis.

A graphical depiction of a proposed model, linking OSA to cardiovascular disease, and the potential role of adhesion molecules, is depicted in Fig. 1. This review will do the following: provide first an overview of the evidence and mechanisms of OSA as an independent cardiovascular risk factor; provide a background on adhesion molecules in atherosclerosis and the process of leukocyte recruitment; synthesize the available literature on adhesion molecules in OSA; identify novel therapeutic modalities that consider cell adhesion molecules as potential therapeutic targets, and also suggest future research directions.

Obstructive sleep apnea, intermittent hypoxia, and cardiovascular disease

Obstructive sleep apnea and cardiovascular disease

OSA is associated with a number of cardiovascular diseases such as heart failure, myocardial infarction, arrhythmias (including atrial fibrillation), systemic and pulmonary hypertension, and stroke.[15–20] It has been suggested that cardiovascular consequences of OSA may appear even in the absence of classical cardiovascular risk factors.[21,22] Thus, OSA has emerged as an independent risk factor for cerebrovascular disease and coronary artery disease.[2,23,24]

Mechanisms for this relationship

There are a number of potential mechanisms for the cardiovascular consequences of OSA, including sleep fragmentation, obesity, and intermittent hypoxia.

Sleep fragmentation. Currently, there is a paucity of studies specifically linking sleep fragmentation to cardiovascular disease risk. Previous studies have found that fragmentation of sleep resulted in increased cortisol secretion,[25] which may be associated with increased sympathetic activation and metabolic changes.[26–28] In addition, fragmentation of sleep has been shown to increase daytime sleepiness, which is a risk factor for a number of medical conditions.[26] Sleep fragmentation was shown to alter responses to

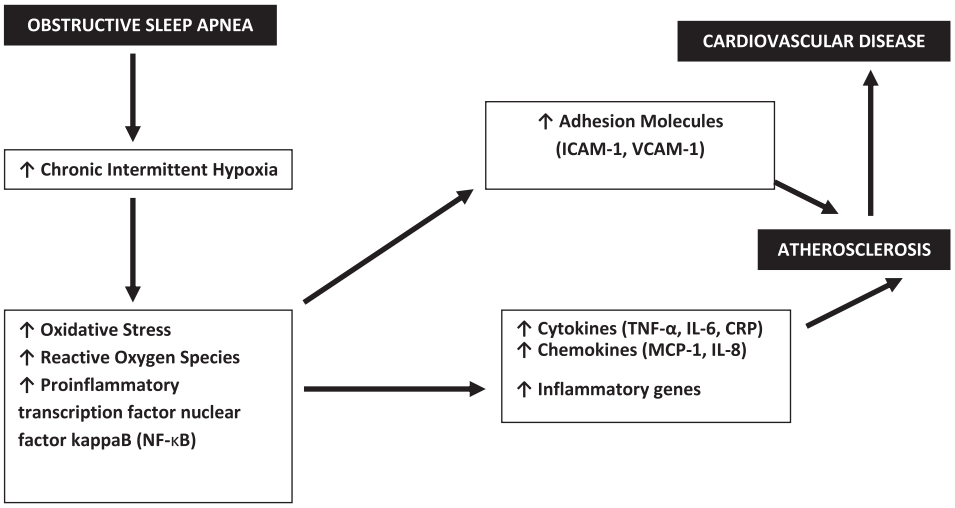

Fig. 1. Schematic illustration of obstructive sleep apnea and the link to atherosclerosis and cardiovascular disease, including the role of adhesion molecules. CRP, C-reactive protein; ICAM-1; intercellular adhesion model-1; IL-6, interleukin-6; IL-8, interleuken-8; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-kappa B; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion model-1.