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Original Article

# Sleep, sleep disorders and inflammation in children

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ABSTRACT

Sleep-disordered breathing (SDB) and, more specifically, obstructive sleep apnea (OSA), can lead to significant morbidities including cardiovascular morbidity and neurocognitive dysfunction in children. Oxidative stress and increased inflammatory process activity are thought to be linked to the morbid consequences of OSA. Clinical and laboratory-based approaches have shown that oxidative stress and inflammation may be further modulated by genetic, lifestyle and environmental factors. Surgical treatment for OSA in children has been shown to be at least partially effective at normalizing endothelial function, reducing levels of inflammatory markers, and improving lipid profile, the apnea–hypopnea index and sleep fragmentation.



## 1. Introduction

Sleep-disordered breathing (SDB), which comprises a spectrum of disorders associated with increased upper airway resistance during sleep, which includes obstructive sleep apnea (OSA), affects up to 12% of prepubertal children [1].

Significant associations between sleep and cognitive development, temperament and behavior have been observed in infants during the first year of life and in school aged children, even when only mild SDB is present [2–5]. Consequently, OSA is now recognized as a major cause of cardiovascular morbidity [6] and neurocognitive dysfunction [7] in children.

Two mechanisms have been proposed to explain the morbid consequences of OSA, namely oxidative stress and increased activation of inflammatory processes [8,9], which may be further modulated by genetic, lifestyle and environmental factors [8,10]. OSA, if left untreated, can result in significant morbidities affecting the central nervous system, cardiovascular and endocrine systems, resulting in a negative impact on quality of life and survival [8,11].

This article will briefly describe sleep disorders and inflammation by reviewing:

- obstructive sleep apnea and cardiovascular morbidity,
- obstructive sleep apnea and cognitive morbidity,
- physiological and inflammatory changes and the effect of treatment on obstructive sleep apnea morbidity,
- factors affecting morbidity in children with obstructive sleep apnea.

## 2. Obstructive sleep apnea and cardiovascular morbidity

Cardiovascular consequences of OSA, which are present in adults, also occur in children. The development of hypoxemia, recurrent arousals and changes in intrathoracic pressures that arise in pediatric OSA can lead to a variety of responses including increased oxidative stress, systemic inflammatory responses, endothelial dysfunction and sympathetic activation, which ultimately manifest as ventricular remodeling, hypertension and atherogenesis (Fig. 1) [12].

The mechanisms underlying the association between OSA and cardiovascular morbidity are uncertain, but oxidative stress, via the production of reactive oxygen species (ROS), and the initiation and propagation of inflammatory processes, have both been proposed as putative mechanisms [13]. The mechanism by which OSA is thought to lead to atherosclerosis is shown in Fig. 2. In this model OSA promotes atherosclerosis via the formation and release of cytokines (including interleukin [IL]-1, IL-6 and tumor necrosis alpha [TNF-α]), leptin and adipokines from adipose tissue; oxidative stress via the increased formation and release of hydrogen peroxide, ROS and reactive nitrogen species, as well as activation of NADPH oxidase; the presence of acute phase reactants such as C-reactive protein (CRP) from the liver; the reduced expression of endothelial nitric oxide synthase (eNOS), increased adhesion molecules and increased apoptosis of endothelial cells; and the activation of platelets. Gozal and Kheirandish-Gozal [13] propose the monocyte as the primordial cell that is markedly affected by conditions of systemic hypoxia-reoxygenation and possibly by other elements of OSA. As shown in Fig. 2, activation of monocytes

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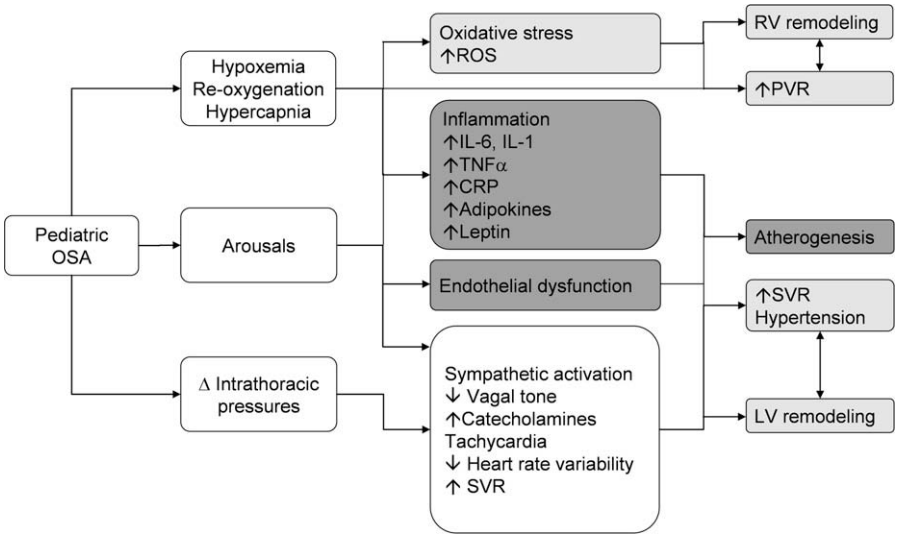




**Fig. 1.** Cardiovascular consequences of obstructive sleep apnea (OSA) in children [12]. CRP = C-reactive protein; IL = interleukin; LV = left ventricle; PVR = peripheral vascular resistance; ROS = reactive oxygen species; RV = right ventricle; SVR = systemic vascular resistance; TNF = tumor necrosis factor. Reprinted from Progress in Cardiovascular Diseases, vol. 51, Bhattacharjee R, et al. Cardiovascular complications of obstructive sleep apnea syndrome: evidence from children. p. 416–33.

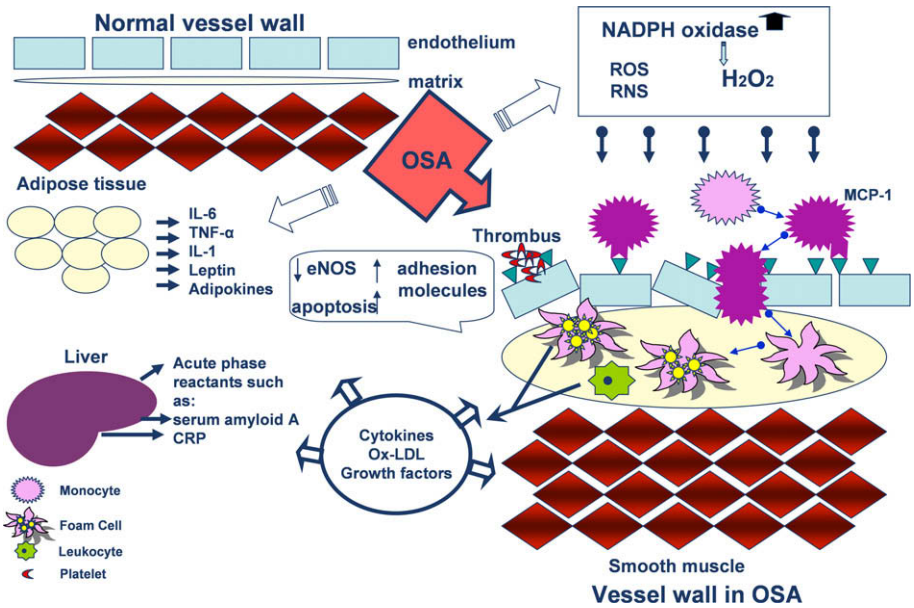




**Fig. 2.** Putative alterations in the normal vessel wall in obstructive sleep apnea (OSA) [13]. CRP = C-reactive protein; eNOS = endothelial nitric oxide synthase; IL = interleukin; LDL = low density lipoprotein; MCP-1 = monocyte chemotactic protein 1; RNS = reactive nitrogen species; ROS = reactive oxygen species; TNF = tumor necrosis factor. Reprinted from Gozal D et al., 2008. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. American Journal of Respiratory and Critical Care Medicine, vol. 177. p. 369–75. Official Journal of the American Thoracic Society.

results in an increase of activated macrophages, causing a cascade of cytokines and growth factors that ultimately promote increased proliferation of smooth muscle in the vessel wall, whilst activated macrophages migrate through the disrupted endothelium into the vessel wall and transform into foam cells, the prototypic cell type of the initial atheromatous lesion. The role of other inflammatory cells, however, such as neutrophils, should not be overlooked [14,15].

Endothelial dysfunction as well as changes to levels of proinflammatory proteins, anti-inflammatory proteins and adhesion molecules have been reported in children with OSA, and will be discussed later in this article.

## 3. Obstructive sleep apnea and cognitive morbidity

Investigation is underway to understand the elements of systemic inflammation and oxidative stress that may play a role in other end organs, e.g., OSA and cognitive functioning.

The effect of OSA on neurocognitive dysfunction has been demonstrated in several studies in mice and rats using the Morris water maze [16–19]. Exposure to intermittent hypoxia (IH) in the absence of sleep deprivation during the resting period of young adult rats (which aims to reproduce reduced oxygen intake commonly observed in moderately severe OSA patients) induced marked increases in cell apoptosis in the hippocampal and cortex regions