Sleep Medicine 15 (2014) 733–741

Contents lists available at ScienceDirect

Sleep Medicine

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

Review Article

Impact of sleep-disordered breathing treatment on upper airway anatomy and physiology

Deepak Shrivastava *

University of California, Davis, CA, USA
Division of Sleep Medicine, Pulmonary and Critical Care, SJGH Sleep Center, 500, West Hospital Road, French Camp, CA 95231, USA

ARTICLE INFO

Article history:
Received 30 July 2013
Received in revised form 7 January 2014
Accepted 14 January 2014
Available online 22 February 2014

Keywords:
Sleep-disordered breathing
Reversibility of inflammation
Continuous positive airway pressure
Mandibular advancement device
Uvulopalatopharyngoplasty
Pharyngeal volume
Obstructive sleep apnea
Apnea–hypopnea index

ABSTRACT

Sleep-disordered breathing (SDB) is a major public health problem. Various anatomic, pathophysiologic, and environmental changes contribute to SDB. The successful treatment of SDB reverses many of these abnormal processes. The present article discusses the current clinical evidence that supports the reversibility and its potential application in the management of SDB. Continuous positive airway pressure reduces angiogenesis and inflammatory edema, increases pharyngeal size, and improves surrogate markers of vascular inflammation and tongue muscle fiber types. Mandibular advancement devices lead to favorable maxillary and mandibular changes, increase pharyngeal area, and improve hypertension. Uvulopalatopharyngoplasty increases posterior airway space and pharyngeal volume, reduces nasal and oral resistance, and lowers response to high CO_2. Weight loss reduces nasopharyngeal collapsibility, critical closing pressure of the airway, apnea–hypopnea index, and improves oxygen saturations. Potential clinical benefits of these changes in the management of SDB and patient compliance with treatment are discussed.

1. Introduction

Obstructive sleep apnea (OSA) is a major public health hazard and is a chronic disease with multiple systemic complications. The prevalence in the United States is estimated to be 10% for 30–49-year-old men, 17% of 50–70-year-old men, 3% for 30–49-year-old women, and 9% of 50–70 year-old women [1]. The consequences of OSA are wide ranging, such as daytime somnolence that interferes with daily function to more severe and potentially life-threatening cardiovascular, neurocognitive, and metabolic complications [2,3].

Therapeutic options in treating OSA have been focused on correcting the mechanical and inflammatory obstruction of the airway, resulting from many anatomical, neuromuscular, and functional pathophysiologic changes. To date, continuous positive airway pressure (CPAP) treatment has the most support for being an effective long-term treatment to affect all of the aforementioned issues and reduce obstructive events. Mandibular advancement devices (MADs), also known as oral appliances (OAs), are common treatments for mild to moderate OSA. Compliance is the main issue surrounding the efficacy of either CPAP or MAD. Group cognitive behavioral therapy may increase the compliance of patients utilizing CPAP [4]. Surgical interventions such as septoplasty, turbinectomy, and uvulopalatopharyngoplasty (UPPP) have been undertaken in an attempt to correct anatomical obstruction of the airways. The risk of perioperative and postoperative complications makes noninvasive modalities more desirable. Adjunctive therapies include weight loss and bariatric surgery. Obesity may cause collapsibility and narrowing of upper airways [5]. Limited studies exist on other novel approaches including positional training, tongue protrusion therapy, and hypoglossal nerve stimulation therapy. At this time, there is inconclusive evidence to support pharmaceutical agents for the primary treatment of OSA. The task of comparing all of these modalities of treatment cannot be easily accomplished because of the variable effectiveness of each modality.

1.1. The effects of CPAP on inflammatory markers

Upper airway inflammation is one of the important intermediary processes leading to airway obstruction. In patients with severe OSA, the surrogate markers of inflammation (interleukin-6 or IL-6) and of oxidative stress (8-isoprostane) are high in the exhaled breath. Tumor necrosis factor-alpha (TNF-α), high-sensitivity

* Address: Division of Sleep Medicine, Pulmonary and Critical Care, SJGH Sleep Center, 500, West Hospital Road, French Camp, CA 95231, USA. Tel.: +1 209 468 7523; fax: +1 209 468 6246.
E-mail address: dshrivastava@sjgh.org

http://dx.doi.org/10.1016/j.sleep.2014.01.002
1389-9457/

C-reactive protein (hsCRP), adhesion molecules, and monocyte chemoattractant protein-1 are high in OSA patients [6–8].

In patients with moderate to severe OSA, the levels of exhaled nasal and oral pentane and nitrous oxide significantly increased after sleep. Pentane is the product of polyunsaturated membrane fatty acid peroxidation by reactive oxygen species (ROS) that induce tissue damage by their effects on the membrane lipids and proteins [9,10].

Increased levels of adenosine and urinary uric acid in OSA patients are implicated with increased production of ROS. This strong association was recently confirmed in a large population from Sao Paulo, Brazil; concluding that an increase in 1 mg/dL in uric acid level was associated with 16% increased risk of OSA (95% C.I. = 1.01–1.33) [11]. Redox-sensitive gene expression is suggested by increase in the protein products like vascular endothelial growth factor (VEGF), erythropoietin, endothilin-1, inflammatory cytokines, and adhesion molecules [12,13].

Treatment of OSA has been shown to change the levels of inflammatory markers favorably [14]. The physiologic and biologic changes mentioned above lead to multisystem complications when the degree of injury outweighs the compensatory mechanisms. The treatment of OSA with CPAP is indeed associated with the reversal of the many biologic abnormalities [15–24].

In one study, CRP and IL-6 levels were higher in patients with OSA compared with obese control subjects (CRP $P < 0.001$, IL-6 $P < 0.05$), confirming the role of inflammatory responses in the development of atherosclerosis and coronary artery disease. CRP induces adhesion molecules on the endothelial cells and chemokine production, while IL-6 plasma level is correlated with mortality rate in patients with coronary artery disease and the risk of developing a myocardial infarction in healthy men. Both CRP and IL-6 levels improved after treatment with CPAP [25–27]. Drager et al. documented the sustained changes that occurred in the histopathology of the vascular system because of OSA and reversal that could be attributed to CPAP treatment. Significant improvement occurred after a treatment period of 4 months with CPAP in patients with severe OSA. The carotid artery intima-media thickness (707 ± 105 μm vs. control group 645 ± 95 μm, $P = 0.04$) and arterial stiffness were measured as pulse wave velocity (10.4 ± 1.0 m/s vs. 9.3 ± 0.9 m/s, $P < 0.001$) between baseline and follow-up. Posttreatment improvement in carotid intima-media thickness ($P < 0.05$) and pulse wave velocity (<0.01) supports the concept that OSA is an independent risk factor for atherosclerosis [28].

In a study by Mansour et al., 6 weeks of therapy with CPAP significantly decreased the levels of CRP, IL-6, and TNF-α in patients with moderate to severe OSA. IL-6 levels before (3.13 ± 0.56) and after CPAP (1.87 ± 0.15, $P < 0.0001$), TNF-α before (7.4 ± 1.29) and after CPAP (4.77 ± 0.96 $P < 0.0001$), and CRP before (0.83 ± 0.1) and after CPAP (0.44 ± 0.18 $P < 0.0001$) were noted [29].

Nural et al. demonstrated that levels of CRP decreased significantly in both the OSA and overlap syndrome patients (patients with OSA and chronic obstructive pulmonary syndrome) who were treated with CPAP for 3–6 weeks. However, in this study, levels of TNF-α and asymmetric dimethylarginine (ADMA) in OSA and overlap syndrome groups did not decrease significantly after treatment with CPAP [30]. A study by Ryan et al. demonstrated no effect on CRP levels after treatment with CPAP (2.29 (1.32–4.10) vs. 2.84 (1.13–5.40) mg/l; $P = 0.145$) [31]. Similarly, a randomized controlled trial by Kohler also documented no decrease in CRP levels with a difference between median changes −0.24 mg/l (95% confidence interval (CI) −0.88 to +0.24); $P = 0.30$) [32].

Although this topic may appear to be controversial, meta-analysis of 10 peer-reviewed studies showed that CRP levels were demonstrated to be reduced (mean decrease of 17.8%, $P = 0.002$) by CPAP treatment. According to the authors, recent studies suggest that CRP elevation in patients with OSA may be independent of obesity [33].

In addition, the level of 8-isoprostane, a marker of lipid peroxidation, which is elevated in OSA patients, reduced after 12 weeks of CPAP treatment (mean 38.5 pg/ml at baseline vs. 22.5 pg/ml on CPAP, $P = 0.0001$) and levels of nitrates, which were decreased in OSA patients, improved (mean 280 μmol/l at baseline vs. 1373 μmol/l post-treatment, $P = 0.0001$) [34].

It has been suggested throughout the reviewed literature that treatment with CPAP for 3–6 months is adequate to document changes in inflammatory marker levels. Many reviewed studies followed a shorter interval, were not controlled, and did not incorporate the confounding effects of smoking history and previous lung or cardiovascular disease [33].

1.2. CPAP treatment and ROS

In OSA, release of ROS from neutrophils in response to hypoxia leads to inflammatory cascades that cause endothelial damage. Neutrophil-reactivated oxygen species has been demonstrated to be correlated with degree of severity of OSA and was found to be independent of obesity [35]. In a prospective case series by Steiropoulos et al., the effect of CPAP on surrogate markers of inflammation was studied. In patients with OSA, the baseline levels of lymphocytes, serum TNF-α, IL-6, and uric acid levels were measured. Repeat levels were obtained after 6 months of treatment with CPAP in one group and from a control group without any intervention. A significant decrease in levels of TNF-α and uric acid levels was noted in the CPAP-compliant (>4 h/night) group. TNF-α levels decreased by a mean of 8.41 ± 5.7 pg/ml vs. baseline 5.72 ± 4.91 pg/ml, $P = 0.001$. Uric acid levels decreased by a mean of 8.79 ± 1.48 mg/dl vs. baseline 6.2 ± 1.37 mg/dl, $P < 0.001$. However, IL-6 levels showed no significant change (2.71 ± 1.27 pg/ml vs. baseline 2.46 ± 1.08 pg/ml, $P = 0.266$) [36].

A controlled study by Barceló et al. in 2006, suggests that CPAP use may ameliorate oxidative stress. Plasma total antioxidant status (TAS), activity of antioxidant enzymes, glutathione peroxidase (GPX) and γ-glutamyl transferase (GGT), antioxidant vitamins (A, E, B_{12}, and folate), and homocysteine levels were compared before and after CPAP treatment. Patients with OSA had lower baseline TAS (1.4 ± 0.16 vs. 1.50 ± 0.10 mmol l^{-1}), vitamin A (64 ± 19 vs. 74 ± 17 μg dl^{-1}) and vitamin E levels (1,525 ± 499 vs. 1,774 ± 503 μg dl^{-1}), and increased values of GGT (42 ± 22 vs. 32 ± 16 U l^{-1}) than controls. There was no difference between groups in GPX, homocysteine, vitamin B_{12}, and folate plasma levels. In the group with OSA, CPAP treatment normalized levels of TAS (1.50 ± 0.13 mmol l^{-1}) and GGT (30 ± 14 U l^{-1}) without effect on vitamin levels [37].

A controlled prospective study by Jelic et al. also suggests that CPAP therapy is associated with the reversal of oxidative stress. In patients with OSA, expression of endothelial nitric oxide synthetase (eNOS) (mean 0.19 at baseline to 0.77 at follow-up) and phosphorylated eNOS increased (from 0.0 to 0.28 at follow-up), whereas expression of nitrotyrosine (1.64–0.35), cyclooxygenase-2 (1.36–0.16), and inducible NOS (0.44–0.20) significantly decreased in patients who adhered to CPAP ⩾ 4 h daily [38].

1.3. Role of CPAP in changing levels of VEGF

Angiogenesis is a known adaptive response to tissue hypoxia [39]. Formation of new blood vessels increases the blood supply to ischemic tissue in an effort to compensate for the decrease in oxygen concentration. VEGF, a key mediator of angiogenesis, is a cytokine that regulates many functions of the vascular endothelial cell. It is upregulated by hypoxic stimulation in cardiac myocytes, vascular smooth muscle cells, and the endothelial cells. VEGF may