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Regular short exposures to cold environment as an adjunct therapy for patients with sleep apnea syndrome (SAS).

Douzi Wafa^{*}, De Bisschop Claire, Dugué Benoit

University of Poitiers, laboratory MOVE (EA 6314), 8 Allée Jean Monnet, faculty of Sport Sciences, 86000 Poitiers, France.

^{*}Corresponding author. Tel.: +33 6 67 29 15 56; fax: +33 5 49 45 33 96

E-mail address: wafa.douzi01@univ-poitiers.fr (W. Douzi).

Abstract:

The sleep apnea syndrome (SAS) is a sleep related-breathing disorder with several features such a systemic inflammation, oxidative stress, a cognitive impairment and a poor sleep quality. Patients with SAS present an increased incidence of cardiovascular diseases. There is no real effective treatment that prevents and treats all of these illness symptoms. Cooling therapies are often used in sport medicine and in athletes after training and competitions to reduce inflammation, oxidative stress and to enhance sleep quality. In this short article, we hypothesize that the use of cooling therapies (whole body cryotherapy, cold-water immersion...) could be an efficient strategy to facilitate the treatment of SAS' patients by reducing the level of systemic inflammation and oxidative stress and enhancing sleep quality.

key words : Cooling, Sleep, Apnea, Hypoxemia, Inflammation, oxidative stress.

Introduction:

The sleep apnea syndrome (SAS) is a sleep related-breathing disorder, characterized by repeated episodes of apnea (cessation of breathing) and hypopnea (decrease in breathing) during sleep [1]. There are three major forms of sleep apnea [2]: the obstructive SAS characterized by intermittent obstruction of the upper airways; the central SAS with a dysfunction in the respiratory control operated by the nervous system, or the mixed SAS that begins with a central disorder followed by an obstructive feature at the end.

Regardless the apnea forms, the repeated awakenings ("arousal") during the nights caused by such apnea induce a deleterious effect on life quality mainly through loud snoring, fatigue, headaches, daytime sleepiness, concentration difficulties and behavior problems [3]. The economic repercussions of SAS are also important due to comorbidities and to the accidents on the public road that it can cause. The SAS features include a systemic inflammation [4], an oxidative stress[5], endothelial dysfunction[6], an increased incidence of cardiovascular diseases[7], metabolic problems[8], and neurocognitive sequelae [9].

Hypoxemia followed by reoxygenation leads to the formation of free radicals causing thereby oxidative stress and participating in tissue inflammation [10]. The endothelial dysfunction and cardiovascular diseases observed in SAS patients may be caused in part by an increased production of reactive oxygen species (ROS) which stimulates the expression of the adhesion molecules (ICAM-1, VCAM-1, E-selectin) leading to microvascular damage [11]. Several studies reported that patients with SAS present an increased oxidative stress with a low concentration of circulating antioxidants such as superoxide dismutase, vitamin E and folic acid and high concentration of circulating homocysteine which is generally linked to increased cardiovascular disease risk [5,11]. To improve sleep quality and reduce oxidative stress, patients with SAS are usually supplemented with antioxidants molecules [11]. Additionally, intermittent hypoxia also leads to systemic inflammation. Therefore, patients with SAS often have an increased level of inflammatory-related biomarkers such as CRP and pro-inflammatory cytokines (IL-1 α , IL-8, IL-6, TNF- α) compared with healthy subjects or SAS patients receiving continuous positive airway pressure (CPAP) treatment [12]. As oxidative stress and systemic inflammation in SAS patients cause endothelial dysfunction and an increase in cardiovascular diseases [13], an elevated apnea hypopnea index is associated with an increased concentration of endothelin-1 (a risk factor for cardiovascular diseases) in blood and a higher level of TNF- α gene expression [14].

Regardless of the severity of the SAS syndrome (mild, moderate or severe), patients have to follow dietetic rules (losing weight in over-weighted and obese subjects as well as avoiding alcohol consumption and smoking, excessive fatigue, hypnotic drugs). In addition, some treatments are recommended such as using **mandibular advancement appliances** [15] in order to eliminate sleep apnea by pushing the lower jaw forward and thus preventing the tongue from folding back and blocking the airway; or using **continuous positive airway pressure (CPAP)** to increase air pressure in the pharynx, preventing thereby the collapse of upper airways [15]. Patients with obstructive SAS can be successfully treated in most cases, following the recommended treatment guidelines [16]. However, the application of CPAP in patients with central SAS is not sufficient to suppress breathing abnormalities and sleep fragmentation [2,17]. It has been recognized [17] that patients with central SAS do not respond to the treatment even though CPAP can improve sleep breathing and prevent airflow limitation, but the central dysfunction persists. Such form of apnea is very complex and there is no real effective treatment able to treat all the symptoms and to prevent underlying complications. We suggest in this paper that the use of cooling therapies could be included as an adjunct therapy to help patients with such SAS who have not responded to CPAP treatment.

The exposure to cold (e.g. winter swimming, cold-water immersion, whole-body cryotherapy) has been shown to reduce inflammation, oxidative stress and to improve sleep quality and well-being following an exercise-induced muscle damage in healthy persons, in athletes and even in patients with inflammatory diseases[18–20]. The repeated exposure to cold has also been shown to reduce oxidative stress and inflammatory status in elderly and obese patients with inflammatory diseases [21–23]. Accordingly, cooling therapies have widely been used in sports medicine to accelerate recovery from muscle injuries due to its anti-inflammatory and analgesic virtues. Furthermore, body cooling (whole body cryotherapy) has been integrated in rehabilitation programs to treat several inflammatory diseases such as rheumatoid arthritis [24]; fibromyalgia [25]; ankylosing spondylitis [26]; multiple sclerosis [27] and even in treating the symptoms of anxiety and depression [28].

Hypothesis:

We hypothesize that regular exposure to cold environment (whole body cryotherapy, cold-water immersion, cold packs, cold showers...) could be included as an

adjunct therapy in SAS (especially central SAS) patients and could prevent the underlying features of the illness such as poor sleep quality, systemic inflammation, oxidative stress, increased sympathetic nervous activity, endothelial dysfunction and cognitive impairment. Cooling therapies are considered safe as they do not seem to negatively affect cardiovascular, immune [18] , and respiratory function [29].

Exposure to cold leads to cold-induced vasoconstriction which reduces skin blood flow, nerve conduction velocity and even attenuates low-grade inflammation [30,31]. It is recognized that regular exposure to very cold air (whole-body cryotherapy) stimulates the immune system and reduces the exercise-induced inflammation response by decreasing the level of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-2, IL-8) and by releasing anti-inflammatory molecules (IL-1ra, IL-10) [32]. Moreover, it has been reported that body cooling could be an effective tool to reduce oxidative stress by stimulating the activity of antioxidant enzymes such as superoxide-dismutase, catalase or glutathione peroxidase, which together neutralize free radicals excess [33,34]. Thus, it can be assumed that these cold-induced effects could help SAS patients to reduce the deleterious effects of repeated apneas, systemic inflammation, and oxidative stress. SAS patients also present an increased sympathetic nervous activity [35] and a poor sleep quality owing to intermittent hypoxia, increased respiratory rate and repeated awakenings at the end of apnea during sleep. Cold therapies (whole body cryotherapy and cold-water immersion) have been shown to stimulate during the cold exposure the sympathetic nervous system, which among others impacts induces the release of noradrenalin but also stimulate in a second phase the activation of parasympathetic nervous activity. Therefore, at distance of the cold exposure a parasympathetic reactivation may occur. This aspect has been observed during the night following a whole-body cryostimulation exposure organized after a late evening physical training. Such feature has been suggested to be responsible for the better sleep quality reported in athletes using cryostimulation [36,37]. The sequence of the events is the following: at the beginning of the cold exposure, the acute cold-induced changes concern peripheral vasoconstriction which induces an increase in central blood volume and in blood pressure [38]. This series of events stimulate arterial and cardiopulmonary baroreceptors, reducing thereby sympathetic nerve activity and increasing parasympathetic activity which leads to a decrease in heart rate [39]. Such feature can also happen at distance from the cold exposure. We have investigated in our previous works [37,40] the impact of whole body cryostimulation on objective and subjective sleep quality in physically active subjects and in athletes after training. The subjects were using (or not using – each subject was his own

control) whole- or partial- body cryostimulation as a recovery procedure after exercise and we observed in the subjects that were using cold exposure that their parasympathetic activity was enhanced in their first slow-wave sleep (SWS) episode during the following night. This reactivation of parasympathetic system at distance of cold exposure could be responsible for the observed improvement in sleep quality [37]. The decrease in sympathetic activity may therefore lead to a lower arousal and may facilitate sleep onset. Hence, the exposure to cold may also help SAS patients to reduce the sympathetic hyperactivity and to improve sleep quality.

The increased sympathetic activity observed in SAS patients is also associated with fluctuations in blood pressure, in heart rate and other cardiovascular complications such as an endothelial dysfunction which is often associated with a reduced nitric oxide (NO) availability in SAS patients [41–43]. Previous works in human [44] and in animal models [45] with SAS showed that **hypoxia**-induced endothelial Nitric Oxide Synthase (eNOS) downregulation may be responsible for the vascular inflammation, the decreased NO availability, the impaired vascular reactivity and thereby leads to an higher risk of cardiovascular diseases in SAS patients. Further, it has been reported in a previous animal model study [45] that long-term intermittent hypoxia in mice with genetic absence of inducible NOS activity induces a proinflammatory response in wake-active brain regions, oxidative injury, and residual hypersomnolence in obstructive sleep apnea. Regular exposure to very cold air (24 sessions of whole-body cryotherapy) has been shown to increase the NOS concentration in elderly subjects regardless of their physical activity level [46]. In another work [47], authors suggested that regular exposure to cold improves the endothelial function through a reduction in inflammatory endothelium parameters (myeloperoxidase activity, serum amyloid A, and sCD40L levels) and in the level of oxidative stress. Accordingly, the exposure to cold have a beneficial impact on human endothelial cells. Hence, the decrease in skin temperature may help SAS patients to enhance endothelial function by decreasing reactive oxygen species production and inflammatory variables levels in endothelial cells. Recently, it has finally been shown that whole body-cryotherapy can increase the concentration of NO in blood due to an increase in the nitric oxide synthase activity at the endothelial level [46].

SAS patients often suffer from metabolic complications such as hepatic steatosis and insulin resistance [48]. In obese patients with SAS, visceral fat is a key element in the inflammatory state [49], and is associated with metabolic imbalance (increase in total cholesterol, LDL-cholesterol, in lipid peroxidation, and a decrease in HDL-cholesterol) and

insulin resistance [50]. In this regard, cold exposure stimulates energy metabolism, especially the lipid metabolism through an activation of adipose tissues to enhance thermogenesis and lipolysis [51]. Further, it has been observed that regular exposure to cold in healthy male subjects (20 sessions of whole-body cryotherapy) induce a decrease in the blood concentration of total cholesterol, LDL-cholesterol, and triacylglycerols, and an increase in the concentration of HDL-cholesterol in blood [52]. Furthermore, it has been demonstrated that cold exposure combined with physical training (winter swimming) reduces the circulating concentration of insulin [53], suggesting thereby the use of cooling strategies in the treatment of non-insulin dependent diabetes [54] and obesity due to its beneficial effects on lipid profile and BMI [55]. These cold-induced metabolic effects might be of importance in the treatment of SAS patients.

Additionally, the poor sleep quality caused by obstructive sleep apnea syndrome may also lead to a cognitive impairment [56] and to decrease executive performances caused by neuronal damages in multiple regions of the brain, but mainly in the frontal cortex [57]. Such situation may be linked with a high risk for early changes in biomarkers for Alzheimer's Disease [56]. Actually, repeated hypoxia in SAS has been shown to induce a cognitive impairment, connected with a rise in biomarkers of neurodegeneration in patients with Alzheimer's disease ($A\beta_{42}$, $A\beta_{40}$, total $A\beta$...) [56]. In a published paper in *Medical Hypotheses* in 2012 [58], it was hypothesized that cold exposure could be an efficient tool to prevent Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD) due to cold-induced anti-inflammatory and anti-oxidative effects. Nine years later, interesting publications in line with what was suggested in this former publication have been published [59–61]. We hope that the hypothesis we are currently presenting concerning the possible effectiveness of regular cold exposures as an adjunct treatment in SAS (especially central SAS) patients will be sooner confirmed by experimental data.

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Conflict of interest statement

None declared.