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TOPICAL REVIEW

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Topical Review

A review of preventing central sleep apnea by inspired CO_2

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Abstract

Although almost completely unknown half a century ago, sleep disorders are gaining recognition as major issues to public health due to their growing prevalence and dire societal consequences. Despite being linked to several infamous catastrophic events such as Chernobyl, it is estimated that 90% of sufferers fail to get diagnosed and receive treatment, and a significant portion of the ones that do are often non-compliant due to the side effects of current treatments. This article presents a review of the current standard treatment for central sleep apnea, and investigates the advantages and possible consequences of using inspired carbon dioxide (CO_2) as an alternative treatment option.

Keywords: sleep disorders, central sleep apnea (CSA), inspired carbon dioxide (CO_2)

(Some figures may appear in colour only in the online journal)

1. Introduction

Although almost completely unknown half a century ago, sleep disorders are becoming a growing health problem. The prevalence and burden of sleep disorders are often overlooked, but their effects are starting to cause notice. There are currently over 80 unique sleep ailments discovered by the International Classification of Sleep Disorders (ICSD), and each has their own treatment plan (Thorpy 1990, American Academy of Sleep Medicine 2001). Some of the most common sleep disturbances include central nervous system hypersomnias, circadian rhythm sleep disturbances, insomnia, sleep-disordered breathing, and sleep-related movement disorders (Panossian and Avidan 2009).

The health effects of these sleep disorders cover a wide range of effects from simple daytime sleepiness, which is very non-specific and common to many disorders (Pagel 2009), to more severe effects such as an increased risk of cardiovascular disease and stroke

(Young *et al* 2002). Approximately 35–40% of people in the United States stuffer from daytime drowsiness (Hossain and Shapiro 2002), which has been shown to lead to reduced cognitive function, a higher prevalence of motor vehicle accidents (Findley *et al* 1988, Dyken *et al* 1996, Marin *et al* 2005), poor work efficiency (Collop 2007, Antic *et al* 2009, Leger *et al* 2012), and is a significant cause of mortality and morbidity (Hossain and Shapiro 2002). It has even been linked to several infamous catastrophic events such as Chernobyl (Hossain and Shapiro 2002), the Challenger explosion, and the Three Mile Island accident (Durning *et al* 2014). As a result, these diseases are now being recognized as major issues to public health due to potentially severe societal consequences (Leger *et al* 2012). Moreover, insufficient or poor quality sleep can influence one's mental status, reducing mental function. This decrease in compliance compounds chronic disease treatment and can aggravate mental conditions such as depression and schizophrenia (Cho *et al* 2008, Wulff *et al* 2012). However, sleepiness is not necessarily always the result of having a sleep disorder. It can also be the consequence of a large sleep debt due to irregular work and/or sleep schedules (Leger *et al* 2012).

2. Diagnosis

The gold standard for the diagnosis of a sleep disorder requires an overnight stay at a sleep laboratory, where the patient is evaluated with a polysomnogram (PSG) (Behar *et al* 2013, Roebuck *et al* 2014). This is more commonly known as a 'sleep study'. The full-night polysomnograms (PSG) are expensive and time-consuming. They require both an open bed at the sleep study center, which can have limited availability due to long waiting lists, and a number of specialists to administer the test and interpret the data (Behar *et al* 2013). Patient expenses can range anywhere from approximately $800 (Deutsch *et al* 2006), to several thousand dollars (Bruyneel *et al* 2011, Masa *et al* 2011, Leger *et al* 2012). There are many sleep recording systems available on the market for home use. They aim to reduce the financial costs in order to reach out and appeal to a larger population; however, in order to cut costs the total number of recording parameters are also reduced (Hesselbacher *et al* 2011, Behar *et al* 2013). Examples of these devices include the type II Sleepscan Netlink Traveller (Bio-Logic Systems, United States of America); the type II Vitaport-4 PSG (TEMEC Instruments, Netherlands); the type IV Visi Grey Flash (Stowood Scientific Instruments, United Kingdom); and the single-channel EEG type IV BioSomnia (OBS Medical, United Kingdom). These devices range from a single-channel data recording system to a 40 channel system (Schweitzer *et al* 2004). However, there is debate whether or not these systems work accurately enough to serve as a diagnostic tool. A patient with no medical guidance or technical training has a greater probability of incorrectly placing the sensors, which can lead to inconclusive or misleading results (Behar *et al* 2013). Even if the data is acquired correctly, there is still a long waiting period to have the results analyzed due to a lack of readily available, trained specialists (Flemons *et al* 2004). Some reject that these home portable sleep monitoring systems are cost advantageous (Reuven *et al* 2001). On the other hand, there are groups that deem that these systems show very good diagnostic accuracy and an excellent alternative to in-laboratory PSG. They claim that patients are more comfortable, which produces better sleep efficiency (Bruyneel *et al* 2011). With the rising trend of risk factors such as obesity, sleep disorders are becoming more common (Inge *et al* 2013, Peppard *et al* 2013, Quan *et al* 2014). Over the last few years, the number of patients being successfully diagnosed and treated has drastically increased (Leger *et al* 2012), but it is still estimated that up to 90% of those affected fail to get diagnosed and receive treatment (Young *et al* 1997).

3. Sleep apnea

One prevalent sleep disorder is sleep apnea; it affects individuals of all ages and is often under-diagnosed (Marcus *et al* 1992, Flemons *et al* 2003). This disease is characterized by breathing that repeatedly stops and starts. The patient undergoes intermittent cessations of breathing (apnoea) or periods with reduced airflow (hypopnea) (Qureshi and Ballard 2003, Behar *et al* 2013). However, sleep apnea can be further categorized into either obstructive sleep apnea (OSA), or central sleep apnea (CSA). Patients with obstructive sleep apnea typically experience a complete or partial block of the upper airway, despite respiratory effort. On the contrary, central sleep apnea is characterized by a lack of drive to breathe (Eckert *et al* 2007, Behar *et al* 2013). Interruptions in respiration, regardless of cause, can lead to insufficient ventilation and consequently compromised gas exchange. Arterial oxygen levels begin to decline while carbon dioxide levels climb (Behar *et al* 2013). Obstructive sleep apnea will not be further discussed in much detail in this article; instead, it will mainly focus on central sleep apnea.

4. Heart failure

Central sleep apnea is extremely common in patients that also suffer from congestive heart failure (CHF) (Javaheri *et al* 1998). Heart failure, a subdivision of cardiovascular disease, is characterized by the progressive weakening of the heart wall. As the condition advances, the heart becomes too weak to eject all the blood from the ventricles, which leads to a decrease in cardiac output and an increase in ventricular filling pressures (Houser *et al* 2012). Over time, the declining cardiac output will fail to meet the body's metabolic needs for oxygen, and the increasing end-diastolic left ventricular volume will cause a buildup of pressure back to the lungs. These alterations in the Starling forces result in excess filtration out of the capillaries (Sieck and Wylam 2014). Ultimately, these pressures lead to increased alveolar fluid in the interstitial space, also known as edema. This pulmonary congestion puts patients at increased risk of developing central sleep apnea due to oxygen's poor solubility (Solin *et al* 1999, Mansfield *et al* 2003, Olson *et al* 2007).

In the United States, heart failure is the leading cause of mortality and morbidity; one out of every eight death certificates mention heart failure as a primary or secondary cause of death. It also is the most frequent cause of hospital admissions in patients over 65 years old (Lloyd-Jones *et al* 2010, Houser *et al* 2012). Over 5.8 million Americans are affected, and 825 000 new diagnosis are being made each year. Readmission rates for such patients exceed 50% within six months, resulting in estimated direct and indirect annual costs of over $39 billion in the United States alone. This amount is vastly underestimated, as it only accounts for cases in which heart failure was the primary diagnosis. Due to the increasing occurrence of biomedical risk factors such as obesity, hypertension, diabetes, and an aging population, the number of people in the United States affected by heart disease is estimated to increase 46% by 2030, with projected annual costs escalating to over $69.7 billion (Lloyd-Jones *et al* 2010, Go *et al* 2014). As many as 50% of patients with heart failure suffer from breathing disorders, the most common being central sleep apnea (Javaheri *et al* 1995, Oldenburg *et al* 2007, Calvin *et al* 2014). As the prevalence of heart failure continues to rise, so will conditions such as sleep apnea. New methods for sleep disorder detection and treatment are needed in order to keep up with the number of people suffering from these diseases.

5. Current treatments

Continuous positive airway pressure (CPAP) is the current gold standard treatment for obstructive sleep apnea. It is also used for patients with central sleep apnea, and has been shown to be especially beneficial for people also suffering from heart failure (Baslas *et al* 2014). At night, the patient wears a mask over their nose and mouth, through which an air blower forces air into the nasal passages. It provides a constant and continuous pressure, but this level can be adjusted. CPAP has been shown to attenuate central sleep apnea, improve nocturnal oxygenation levels, and improve the ejection fraction of the heart. They are moderately effective when used correctly, but due to side effects, approximately 30–35% of patients are intolerant or non-compliant. These side effects can include skin abrasions, bruising, chafing, abdominal cramping, chest discomfort, and nasal congestion or dryness (Guilleminault and Abad 2004). Even compliant patients typically use it for less than the optimal duration necessary to prevent adverse outcomes; anywhere from 29–83% of patients use the CPAP for less than four hours per night. Studies have demonstrated a dose dependent relationship with CPAP use and symptom improvement and lowered mortality (Weaver *et al* 2007), and failure to use the device for even a single night can permit the reemergence of daytime sleepiness or neurobehavioral deficits (Weaver and Grunstein 2008). Studies have also shown lowered norepinephrine levels and improvements in the six-minute walk test (6MWT) with use of a CPAP (Bradley *et al* 2005). This standard test is used to evaluate the integrated response of the pulmonary, cardiovascular, and circulatory systems, in addition to neuromuscular control and muscle metabolism; however, it cannot provide the relative contributions of each of these systems (Laboratories 2002, Impens *et al* 2008). Overall, CPAP has been shown to reduce some of the negative pathophysiologic consequences of CSA, but it is unclear whether these improvement are due to the elimination of CSA itself or due to the CPAP improving cardiac function (Bradley *et al* 1992).

Another treatment method for CSA is the adaptive servo-ventilation machine (ASV). It is very similar to the CPAP machine in that it also delivers pressurized room air into the patient's nose and mouth through a mask. However, the major difference is that ASV therapy uses an algorithm in order to support regular breathing. It is sensitive enough to detect significant reductions or pauses in the breathing rhythm, and fluctuate its pressures in order to support each individual breath. Several studies have shown that ASV is superior to CPAP in patients with heart failure with respect to sleep quality, overall number of heart failure events, and that it may even contribute to the prevention of increased mortality rates (Arzt *et al* 2015, Macedo *et al* 2015). However, the effectiveness and safety of this treatment method is currently under debate. It has been shown to be ineffective in patients with sleep apnea that is complicated by chronic opioid therapy (Farney *et al* 2008), as well as possibly increasing the mortality rate of individuals with chronic heart failure in conjunction with a reduced left ventricular ejection fraction (LVEF $\leqslant 45\%$) (American Academy of Sleep Medicine 2015, Cowie *et al* 2015). However, some groups argue that there was substantial non-adherence to the study protocol regarding the patients' use of the ASV, and that carefully monitored trials should be encouraged to further investigate the effectiveness of ASV in heart failure patients (Bradley *et al* 2016).

Even though it has been over a century since pathological Cheyne–Stokes breathing was shown to be abolished by the administration of excess carbon dioxide (CO_2) (Douglas and Haldane 1909), the potential systemic consequences of hyperventilation and sympathetic overactivation that could make this a less attractive treatment option are still being studied (Andreas 1998, Lorenzi-Filho 1999). One study reported that the overall number of sleep-related arousals were not reduced and overall sleep quality was not altered, even though static CO_2 delivery reduced the number of oscillations in ventilatory parameters (Szollosi 2004). It is possible that the excess CO_2 could be directly stimulating the cortex, or reducing the cortical arousal threshold.

6. Chemical control of breathing

Chemoreceptors are sensory receptors responsible for transducing chemical signals into action potentials that the brain can interpret and regulate. There are two main classes, the peripheral chemoreceptors (located in the aortic body on the transverse aortic arch and on the carotid body on the common carotid artery) and the central chemoreceptors (which are located on the ventrolateral surface of the medulla oblongata in the central nervous system) (Kirkman 2008). Together they are responsible for regulating the body's pH, Pa_{O_2}, and Pa_{CO_2} levels within their physiological set points. The central chemoreceptors are unable to respond to plasma changes in hydrogen ion (H^+) as the peripheral chemoreceptors can, since H^+ is unable to pass the blood–brain barrier. Instead, these neurons measure the pH change of the cerebral spinal fluid (CSF) due to Pa_{CO_2}. The CSF acidity is influenced solely by changing carbon dioxide levels, which is able to pass through the blood–brain barrier. As the CO_2 diffuses across, it reacts to form carbonic acid which quickly dissociates into bicarbonate and hydrogen ions, effectively decreasing the local pH. Due to its influence on pH levels, Pa_{CO_2} is very closely monitored through a negative feedback mechanism to a set point of approximately 5.3 kPa, or 40 mmHg in a healthy individual (Kirkman 2008).

The respiratory system is able to compensate for small deviations in plasma pH by altering the respiratory rate. An increase in Pa_{CO_2}, for example, will be sensed by the chemoreceptors and the patient will undergo a period of hyperventilation, resulting in the excess exhaling of CO_2, which is present in the blood. Even a small rise can recruit upper airway dilator muscles in order to prevent airway obstruction (Dempsey *et al* 2010, 2014). However, these ventilation output changes can vary greatly between various individuals and with different diseases (Eckert *et al* 2007). An individual with high chemosensivity will over respond to these small changes in chemical stimuli and continue to hyperventilate until the Pa_{CO_2} falls below the eupnic level and the pH becomes too basic. They then will begin to hypoventilate in order to retain CO_2 and decrease pH back to normal. Individuals suffering from CSA and heart failure typically present with increased sensitivity to CO_2 (Solin *et al* 2000). The mechanism responsible for this heightened chemosensitivity is believed to be increased sympathetic activity, as measured by urine (Naughton *et al* 1995, Solin *et al* 2003), plasma (Naughton *et al* 1995), direct skeletal muscle activity, and norepinephrine levels (Mansfield *et al* 2003). Similarly, low chemosensitivity can be just as destabilizing, as severe blood gas disturbances can occur before a respiratory response is observed (Eckert *et al* 2007). All individuals, healthy or otherwise, are susceptible to breathing cessation if the Pa_{CO2} falls below a threshold denoted as the apnea threshold. This threshold is typically about 2–6 mmHg below the eucapnic sleeping Pa_{CO_2} levels (Dempsey 2005, Eckert *et al* 2007).

7. Inspired CO_2

The use of CO_2 to stabilize periodic breathing abnormalities has been investigated since the early 1980s (Berssenbrugge 1983). Since then, several other studies have reported that use of constant CO_2 inhalation was able to help prevent apneas so long as enough CO_2 was administered (Badr 1994, Steens and Millar 1994, Xie 1997, Lorenzi-Filho 1999). It is believed that chemoreceptor oversensitivity is the mechanism resulting in the periodic reductions in Pa_{CO_2} below the apnea threshold that causes the cessation of breathing in central sleep apnea. It is not known if this is triggered mainly by the peripheral or central chemoreceptors (Lorenzi-Filho *et al* 1999), but it is hypothesized that breathing in low concentrations of CO_2 at night can eliminate these apneas. This alternative therapy, if successful, would provide a new treatment for patients where CPAP had failed, or was intolerable.

There have been many short term studies showing that inspired CO_2 has been successful in treating CSA patients with CHF (Steens *et al* 1994, Lorenzi-Filho *et al* 1999, Giannoni *et al* 2010), without CHF or any other apparent cardiovascular adverse effects (Xie *et al* 1997, Khayat *et al* 2003), with idiopathic central sleep apnea (ICSA) (Xie *et al* 1997), and with Cheyne–Stokes breathing (CSB) (Lorenzi-Filho *et al* 1999). Overall breath-to-breath oscillations of Pa_{CO_2} stabilized, as well as pH, overall breathing rhythm (Khoo *et al* 1982), and overall CSA symptoms (Szollosi *et al* 2004). However, the delivery system from exogenous CO_2 is quite cumbersome and not easy to manage in a household setting. Some reports even show that increased CO_2 inspiration does not improve sleep quality (which is most commonly due to the tight face mask) (Steens *et al* 1994), has no reduction in the number of arousals during sleep (Szollosi *et al* 2004), and may lead to increases in sympathetic excitation (Andreas *et al* 1998).

Other studies have been performed investigating ways to increase CO_2 without the use of CO_2 tanks. One possible alternative is adding additional dead space. Dead space is the volume of airway passages (such as the trachea and bronchi) which contain air that does not reach the alveoli, where it must reach if it is to contribute to gas exchange. By adding a mask attached to a small cylinder, less carbon dioxide is exhaled in each breath and the total distance to the lungs is increased; in other words, dead space is added. The rebreathing of this carbon dioxide induces moderate hypercapnic (increased CO_2) conditions. The addition of approximately 400–600 ml of dead space has been shown to decrease the Apnoea–Hypopnoea index (AHI) (which is represented by the number of apnea and hypopnea events per hour of sleep), decrease the number of arousals, improve sleep quality (Khayat *et al* 2003), and stabilize breathing patterns (Xie *et al* 2001, 2013). However, there may be adverse effects to adding dead space. This includes fatiguing already compromised respiratory muscles, and inducing sympathetically driven responses such as vasoconstriction, tachycardia, and increased myocardial contractility. Overworking the heart may lead to an increase in morbidity (Khayat *et al* 2003).

Furthermore, some other clinical studies have reported the effect of low concentrations of inhaled CO_2 in a group of preterm infants with apnea. The premature infants can respond to CO_2 inhalation with an overall decrease in total pulmonary resistance, which allows them to achieve greater airflow (Miller *et al* 1991). Al-Saif *et al* (2001) found that low concentrations of CO_2 (0.5%–1.5%) decreased the total number and the duration of apneas, a mild increase in the minute ventilation, and improved oxygenation. Moreover, they suggest that a 0.8% CO_2 concentration in preterm infants is just as effective as theophylline treatments, but with fewer side effects (Al-Saif *et al* 2008).

8. Conclusions

In summary, the number of sleep apnea diagnoses is rapidly increasing each year due to more awareness and better detection instruments. The prevalence of this disease is going to keep increasing as heart failure, to which is it closely tied with, continues to plague more of the human population. Particularly in developed countries that have increased life expectancies. The current gold standard for the treatment of sleep apnea, CPAP, does not always work with patients with central sleep apnea and a significant portion of those it would help refuse to utilize it due to its side effects and an inability to sleep with the mask. There have been several promising studies showing that inspired CO_2 (either directly inspired through exogenous tanks or by increasing the total dead space) can help reduce the AHI and improve sleep quality compared to CPAP. However, there are several potential adverse effects associated

with inspired CO_2 that have not been fully explored. The initial results from the short trials are promising, but larger studies are needed to determine the long-term efficacy and safety of inspired CO_2 as a possible treatment for CSA.

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