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Chemoreflex Physiology and Implications for Sleep Apnea – Insights from Studies in Humans

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Abstract

Activation of the chemoreflex in response to hypoxemia results in an increase in sympathetic neural outflow. This process is predominantly mediated by the peripheral chemoreceptors in the carotid bodies and is potentiated by the absence of the sympatho-inhibitory influence of ventilation during apnea, as is seen in patients with sleep apnea. In these patients, repetitive nocturnal hyoxemia and apnea elicit sympathetic activation, which may persist into wakefulness, and is thought to contribute to the development of systemic hypertension, and cardiac and vascular dysfunction. Chemoreflex activation could possibly lead to adverse cardiovascular outcomes such as nocturnal myocardial infarction, systolic and/or diastolic heart failure, cardiac arrhythmias and sudden death in patients with sleep apnea. This review summarizes chemoreflex physiology in health and disease, with specific focus on chemoreflex-mediated pathophysiology in obstructive and central sleep apnea. Measurement of the chemoreflex response may serve as a potential avenue for individualized screening for cardiovascular disease. Whether modulation of this response in sleep apnea may aid in the prevention and treatment of adverse cardiovascular consequences will require further study.

Keywords

sleep disordered breathing; sympathetic; consequences

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Author contributions

Meghna P. Mansukhani drafted and revised the manuscript.
Shihan Wang revised the manuscript.
Virend K. Somers created the outline, drafted and supervised the writing of the manuscript.
All authors confirm that they have approved the final version of this manuscript. All persons designated as authors qualify for authorship and all those who qualify for authorship are listed.

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Competing interests

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Chemoreflex physiology

Hypoxemia elicits increases in ventilation with modest accompanying increases in sympathetic nerve traffic to blood vessels (Somers *et al.*, 1989b, a; Somers *et al.*, 1991). At the same time, inspiration and stretch of thoracic afferents have an inhibitory or buffering influence on the autonomic response to hypoxemia, so that during hypoxemia the increase in sympathetic activity is masked by the accompanying hyperventilation. Importantly, the primary response to hypoxemia is bradycardia mediated by increased cardiac vagal outflow, a response also suppressed by ventilation and activation of thoracic afferents (Angell-James & Daly, 1975; Somers *et al*. 1989b, a; Somers *et al.* 1995). Hence when hypoxemia is accompanied by apnea, the adaptive sympathetic and vagal responses become more evident, manifesting as potentiated sympathetic vasoconstriction and vagal bradycardia (Kara *et al.*, 2003). This simultaneous activation of central sympathetic outflow to blood vessels and vagal outflow to the heart constitutes part of what is known as the “diving reflex” (Angell-James & Daly, 1975), a reflex that is exhibited strongly in aquatic mammals such as sea lions. The concurrent responses to hypoxemia including peripheral vasoconstriction and bradycardia enable these air breathing mammals to stay under water for extended periods.

In humans, hypoxemia and apnea occur both in physiologic conditions such as swimming and pathologic conditions such as sleep apnea (Somers *et al.*, 2008). The clinical implications of the chemoreflex response to hypoxemia are discussed further later in this review.

Hypoxemia acts primarily through the peripheral chemoreceptors in the carotid sinus. While hypercapnia influences both the carotid body as well as central chemoreceptors in the medulla oblongata, there is evidence that the peripheral chemoreceptors, through afferent innervation, act to enhance the effect on the sensitivity of central chemoreceptors to hypercapnia (Kara *et al.*, 2003; Blain *et al.*, 2010; Del Rio *et al.*, 2010). Hypercapnia also elicits increases in sympathetic outflow to peripheral blood vessels and this response is buffered by hyperventilation. The combination of hypoxemia and hypercapnia results in a potentiated sympathetic response and during apnea, due to the co-occurrence of hypoxemia and hypercapnia in the absence of ventilation, the sympathetic activation can increase synergistically (Somers *et al.*, 1989b).

The peripheral chemoreflex responses are potentiated by catecholamines which activate receptors in the carotid bodies (Heistad *et al.*, 1974). Dobutamine, a beta-1 agonist, has been found to enhance the ventilatory and autonomic effects of the chemoreflex in healthy human subjects (Velez-Roa *et al.*, 2003). In addition, angiotensin II, which in turn is increased as a result of sympathetic activation from hypoxemia, can directly stimulate sympathetic nuclei located in the hypothalamus and brainstem. Many studies have demonstrated that endogenous nitric oxide (NO) plays an important role in the carotid body chemoreceptor function as an inhibitory modulator (Pimenta *et al.*, 2013). Production of pro-inflammatory cytokines (Del Rio *et al.*, 2012) reactive oxygen species and differential expression of hypoxia–inducible factors 1 & 2 in the carotid bodies (Mansukhani *et al.*, 2014) have recently been demonstrated in animal and human studies.

Activation of the baroreflexes has an inhibitory influence on chemoreflex gain, with inhibition of the response to hypoxemia being more marked than inhibition of the response to hypercapnia. Activation of the baroreflex is able to inhibit both ventilatory and autonomic responses to chemoreflex activation (Somers *et al.*, 1991; Somers *et al.*, 1992; Narkiewicz *et al.*, 1998b). Interestingly, bradyarrhythmias induced by hypoxemia and apnea are attenuated when the baroreflexes are activated simultaneously. This speaks to the power of the reflex interaction since baroreflex activation itself induces bradycardia; thus, in the absence of an inhibitory influence from normal ventilation, rather than being unchanged or increased, the bradycardic response to chemoreflex activation is attenuated by simultaneous baroreflex activation (Somers *et al.*, 1991; Somers *et al.*, 1992).

These data would suggest that disease conditions that are associated with impaired baroreflex gain, such as hypertension and heart failure (Somers *et al.*, 1991; Somers *et al.*, 1992) would also be accompanied by exaggerated chemoreflex responses.

Peripheral Chemoreflexes in Hypertension

There is evidence suggesting potentiation of the peripheral chemoreflex in spontaneously hypertensive rats (Fukuda *et al.*, 1987) and that the autonomic disturbance precedes the onset of hypertension (Iturriaga *et al.*, 2010). An exaggerated ventilatory response to hypoxemia has also been noted in borderline hypertensive humans (Trzebski *et al.*, 1982). Measures of peripheral sympathetic traffic have confirmed this heightened response to hypoxemia in borderline hypertension and demonstrated that the potentiated chemoreflex-mediated sympathetic vasoconstriction was especially striking when apnea was superimposed on hypoxemia (Somers *et al.*, 1988).

Chemoreflexes in Obesity

In order to better determine the role of the chemoreflex in disease conditions, it is important to understand the physiology of the chemoreflex in conditions such as obesity and aging, and the influence of gender. Studies in obese humans who are free of any co-existing disease show that obesity is associated with a heightened central chemoreflex response to hypercapnia. This appears to be a selective potentiation, since the response to hypoxemia is not different from that seen in normal weight control subjects (Narkiewicz *et al.*, 1998a). The mechanism underlying this selective central chemoreflex potentiation is unclear, but may be related to the effect of leptin, which is produced by the adipocytes and increased in conditions such as obesity (Ciriello & Moreau, 2012). These findings may shed some light on understanding the higher baseline sympathetic nerve activity in OSA subjects with metabolic syndrome compared to those without metabolic syndrome (Mansukhani *et al.*, 2014).

Sympathetically mediated renal vasoconstriction in response to voluntary apnea was not found to be different between healthy young and older subjects in a recent study (Patel *et al.*, 2013), although evidence on the effects of aging on the peripheral chemoreflex from previous studies is equivocal (Poulin *et al.*, 1993; Schmidt *et al.*, 2005). The results of another study by Patel et al. suggested that female sex hormones could dampen the effects of sympathetic vasoconstriction in the forearm induced by apnea under experimental

conditions (Patel *et al.*, 2014). The effect on control of breathing in pre- and post-menopausal women may be mediated by the central rather than the peripheral chemoreflex, in addition to female sex steroid hormones (Preston *et al.*, 2009).

Obstructive Sleep Apnea

Patients with obstructive sleep apnea (OSA) have a selective enhancement of the ventilatory and autonomic responses to hypoxemia, but not to hypercapnia. The autonomic responses, specifically, peripheral sympathetic vasoconstriction and vagally mediated bradycardia, are especially evident during apnea (Narkiewicz *et al.*, 1998b; Iturriaga *et al.*, 2005). This selective enhancement in peripheral chemoreflex gain is not explained by hypertension alone, since the responses described above were manifest in normotensive OSA subjects (Narkiewicz *et al.*, 1998b). Furthermore, although patients with OSA are often obese, the chemoreflex physiology appears to differ from that seen in obesity, where it is the chemoreflex response to carbon dioxide that is accentuated (Narkiewicz *et al.*, 1999).

Patients with OSA undergo repetitive episodes of hypoxemia and sometimes hypercapnia during disordered breathing events. Consequently, during these obstructive breathing events sympathetic vasoconstriction is striking, with increases in blood pressure to very high levels (Figure 1). While simultaneous bradycardia is often evident, especially toward the end of an apnea, some patients develop severe bradyarrhythmias including Mobitz type II, complete heart block, and even asystole lasting for 10 seconds or more (Somers *et al.*, 1995). This bradyarrhythmic response is more frequent in those who experience more profound nocturnal oxygen desaturation (Koehler *et al.*, 2000) and is mediated via the chemoreflex. Thus, the first line of treatment is prevention of apnea rather than placement of a permanent pacemaker.

Recent studies have suggested that vascular factors, sleep deprivation and impaired exercise tolerance could also play a role in the sympathetic activation seen in OSA (Mansukhani *et al.*, 2014).

The chemoreflex-mediated neural circulatory responses to OSA have other wide ranging consequences. These include first, that the physiologic fall in blood pressure during sleep is attenuated or abolished, resulting in a “non-dipper” blood pressure profile. These patients, whose blood pressure does not fall at night, are known to be at increased long-term risk for cardiovascular disease (Endeshaw *et al.*, 2009). Not only has OSA been found to be closely associated with baseline hypertension and incident hypertension in a dose-dependent fashion but has also been noted to be the most common secondary cause of increased blood pressure in subjects with resistant hypertension (Mansukhani *et al.*, 2014).

Second, the hypoxemia occurring in the setting of hypercapnia, increased sympathetic drive, and other apnea induced stresses, is known to elicit cardiac ischemia with accompanying ST segment changes (Mooe *et al.*, 2000), and may also contribute to the increased likelihood of nocturnal myocardial infarction in patients with OSA (Kuniyoshi *et al.*, 2008).

Third, simultaneous sympathetic and vagal activation in the setting of hypoxemia may increase the likelihood of atrial fibrillation and may also explain, at least in part, the

increased risk of potentially lethal arrhythmias occurring at night requiring the appropriate firing of implanted cardiac defibrillators (Zeidan-Shwiri *et al.*, 2011). Additionally, the increased likelihood of cardiac ischemia and cardiac arrhythmias are likely contributors to the heightened risk for nocturnal sudden death in patients with OSA (Gami *et al.*, 2005) (Figure 2).

Treatment of OSA with CPAP, tracheostomy and oral appliances has been shown to decrease urinary and serum catecholamine levels, muscle sympathetic nerve activity, nighttime and 24-hour blood pressures (Mansukhani *et al.*, 2014). Those with comorbid diabetes mellitus and severe OSA appear to demonstrate a greater decline in catecholamine levels. Decreases in 24-hour mean blood pressure have also been noted in subjects with pre-hypertension and resistant hypertension after long-term CPAP use in some recent studies (Mansukhani *et al.*, 2014).

Central Sleep Apnea

Central sleep apnea (CSA) occurs predominantly in patients with heart failure, where it may sometimes manifest as a crescendo-decrescendo breathing pattern called Hunter Cheyne Stokes breathing(Javaheri & Corbett, 1998). Patients with heart failure also have a propensity towards heightened sensitivity to arterial carbon dioxide (PaCO2). It is thought that this heightened PaCO2 responsiveness may be an important factor underlying the unstable breathing pattern that results in central apneas during sleep in heart failure patients (Javaheri & Corbett, 1998).

Although patients with systolic and diastolic heart failure have high levels of sympathetic drive at baseline, during central apneas sympathetic outflow increases even further (van de Borne *et al.*, 1998). In heart failure patients with CSA, plasma and urinary catecholamines are higher than in heart failure patients without CSA (Mansfield *et al.*, 2003; Solin *et al.*, 2003). Interestingly, the increased sympathetic activity appears to be related to heart failure severity and not CSA severity (Mansfield *et al.*, 2003). This increase in adrenergic drive in heart failure patients with CSA may help explain, in part, the increased mortality risk in this patient population (Levy *et al.*, 2013).

Lanfranchi et al. reported autonomic dysfunction, as measured by decreased heart rate variability, in patients with CSA (Lanfranchi & Somers, 2003). Additionally, treatment of OSA with CPAP in patients with congestive heart failure has been shown to reduce this autonomic dysfunction (Gilman *et al.*, 2008). In a study of 216 patients with stable advanced heart failure, with 21 (9%) patients suffering a cardiac arrest over a 4-year follow up period, the most common electrocardiographic rhythm preceding sudden cardiac arrest was noted to be severe bradycardia, which is frequently seen in patients with OSA (Luu *et al.*, 1989). While these studies reveal some preliminary insights into the potential mechanisms which may result in increased mortality in heart failure patients with coexistent CSA/OSA, studies to further elucidate and confirm these findings are required.

Conclusions

Chemoreflex physiology is important in maintaining homeostasis, particularly during physiologic stresses such as swimming and ascent to higher altitude. However, in pathological conditions, the activity of the chemoreflex may be abnormal and may contribute to cardiovascular pathophysiology and adverse outcomes. Recognition of the role of the chemoreflex in disease and the mechanisms by which the chemoreflex may potentiate adverse events may allow us to identify strategies for both prevention and treatment. Novel methods to quantify and alter the chemoreflex response in sleep apnea may help individualize these prevention and treatment strategies.

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NEW FINDINGS

What is the topic of this review?

This review summarizes chemoreflex physiology in health and disease with specific focus on chemoreflex-mediated pathophysiology in obstructive and central sleep apnea.

What advances does it highlight?

Chemoreflex mechanisms are thought to contribute significantly to the pathophysiology and adverse outcomes seen in sleep apnea. Clinical implications of altered chemoreflex function in sleep apnea from recent studies in humans, including cardiac arrhythmias, coronary artery disease, systolic/diastolic heart failure as well as sudden cardiac death are highlighted.

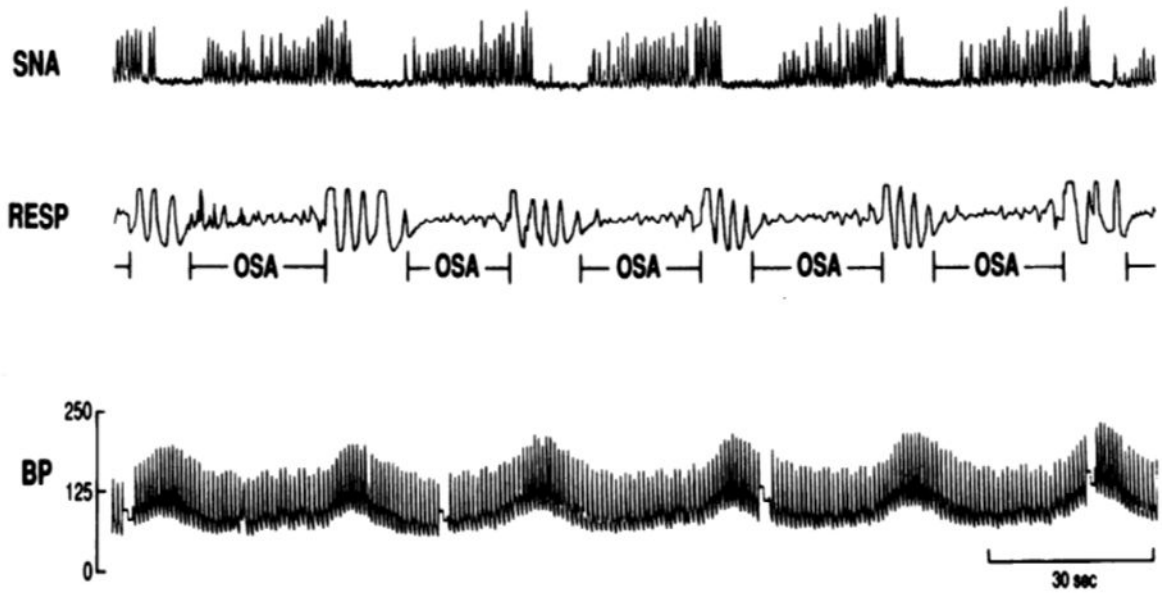

Figure 1.

Recordings of sympathetic nerve activity (SNA), respiration (RESP) and blood pressure (BP) during 3 minutes of non-rapid eye movement sleep, showing significant oscillations in SNA and BP in response to obstructive sleep apnea (OSA).

Reproduced with permission from Somers *et al.* 1995 (Somers *et al.*, 1995).

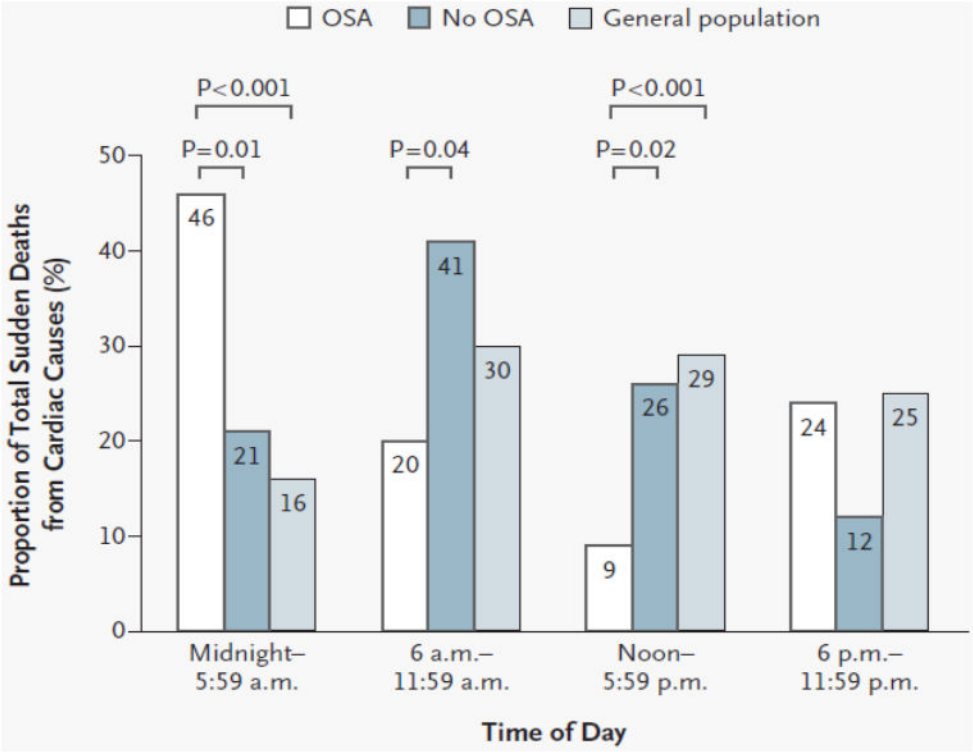

Figure 2.

Day-night pattern of sudden cardiac death in subjects with obstructive sleep apnea (OSA), without OSA and in the general population.

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