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Review

Obstructive sleep apnea syndrome and autonomic dysfunction

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ABSTRACT

Autonomic nervous system (ANS) has been extensively explored in obstructive sleep apnea (OSA).

Autonomic alterations in these patients have been described by means of several methods, evaluating ANS function both directly with microneurography and indirectly through baroreflex sensitivity (BRS, by the sequence method or the cross-spectral approach), heart rate variability analysis (HRV, both in the time and frequency domain) during sleep and wake, or conventional laboratory tests, including cold pressor test, hand grip test or measurement of urinary cathecolamine excretion.

Several studies in OSA patients have shown ANS alterations, in particular sympathetic overactivity, both acutely during apnea events and chronically during the daytime, being both also involved in cardiovascular consequences of sleep disordered breathing.

The association between OSA and sympathetic dysregulation suggests a dose response relationship between OSA severity and the degree of sympathetic overactivity and this association seems to be reversible as the treatment of OSA is implemented.

Additionally ANS is involved in regulating visceral and humoral functions to maintain the body homeostasis and in reaction and adaptation to external and internal stressor stimuli.

However, the vast majority of studies have focussed on cardiovascular alterations, which are easier to measure, somewhat neglecting the other functions regulated by ANS.

More evidence is therefore needed to better characterize the impact that sleep disorder breathing may have on ANS both in the short and long term.

1. Introduction

Autonomic nervous system (ANS) dysregulation has been extensively explored in obstructive sleep apnea (OSA) and has been recognized as one of the most important pathogenetic mechanisms for cardiovascular consequences of sleep disordered breathing. Several studies in OSA patients have shown that repetitive upper airways obstructions and intermittent hypoxia/hypercapnia through the resulting chemoreflex activation, are responsible for a sympathetic overactivity, both acutely during apnea events and chronically during the daytime. Autonomic alterations in these patients have been described by means of several methods, evaluating ANS function both directly with microneurography and indirectly through baroreflex sensitivity (BRS, by the sequence method or the cross-spectral approach), heart rate variability analysis (HRV, both in the time and frequency domain) during sleep and wake, or conventional laboratory tests, including cold pressor test, hand grip test or measurement of urinary cathecolamine excretion) (Parati et al., 1988; Parati et al., 1995; Parati et al., 2000; Cortelli et al., 1994; Bisogni et al., 2016).

According to the Bradford-Hill criteria, the association between OSA and sympathetic dysregulation seems biologically plausible and consistent (Dimsdale et al., 1995) with a dose response relationship between OSA severity and the degree of sympathetic nervous system (SNS) activation (Elmasry et al., 2002).

Moreover, the association seems to be reversible as the treatment of OSA has been shown to reduce sympathetic overactivity and this has been neatly demonstrated in both cross sectional studies and withdrawal studies (Kohler et al., 2011).

However, demonstrating that ANS functioning is affected by sleep disordered breathing with a carryover effect during the daytime is challenging. In the present narrative review we will critically discuss available literature on this topic.

2. Changes of ANS and corresponding cardiovascular alterations in OSA

Since the seminal studies by the Bologna group in the early seventies, demonstrating for the first time that intermittent partial or complete upper airways obstructions at night were associated with fluctuations of blood pressure and heart rate (Coccagna et al., 1972), several other studies worldwide confirmed these findings, describing also the typical non dipping blood pressure profile in OSA patients and

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analyzing the potential role of the ANS in the pathogenesis of hypertension and cardiovascular complications related to sleep disordered breathing.

The acute effects of obstructive events are characterized by heart rate (HR) and BP reductions during an apneic event, where there is a predominance of parasympathetic activity, followed by the typical HR and BP surges at the end of the event with the recovery of airway patency. Although several different pathophysiological pathways are implicated in the development of OSA-related BP surges, strong evidence is available supporting the view that during OSA events an increase in sympathetic activity plays a significant role, being the consequence of chemoreceptor stimulation, arousals from sleep and activation of pulmonary stretch receptors.

Apnea-related changes in ANS activity have been demonstrated in different studies using various techniques. The Mayo Clinic group focussed on microneurography, where a tiny (about 100–200 μm in diameter, with a tip diameter of about 1 μm) tungsten microelectrode, with an epoxy resin-insulated shaft (impedance around 1–5 MΩ at 1 kHz), is directly inserted in human peripheral myelinated and unmyelinated efferent and afferent fibres of muscle and skin nerves. The recording of efferent discharges in post-ganglionic sympathetic C efferent fibres innervating muscles (muscle sympathetic nerve activity, MSNA) and skin (skin sympathetic nerve activity, SSNA) provides information on the neural control of autonomic effector organs, including blood vessels and sweat glands. Somers and colleagues showed that: 1) MSNA alterations were associated with blood pressure fluctuations before, during and after an apneic event, 2) such alterations were independent of obesity but only related to sleep apnea and 3) CPAP could decrease daytime sympathetic traffic in OSA patients (Narkiewicz et al., 1998; Narkiewicz et al., 1999; Somers et al., 2008).

Our group extensively explored baroreflex sensitivity (BRS) in OSA patients by applying the “sequence technique method (Parati et al., 1988).

The baroreflex is considered to be the first important relay in the integration between cardiovascular reflexes and central autonomic influences. The arterial baroreceptors are mechanoreceptors located in the carotid sinuses and aortic arch, innervated by the glossopharyngeal and the vagus nerves. Such receptors are stimulated by changes in carotid or aortic wall stretch elicited by rises or falls in arterial pressure. Primary baroreceptor afferents provide excitatory input to the nucleus of the solitary tract (NTS) which is characterized by two efferent pathways: a sympathoinhibitory pathway from the NTS to sympathoexcitatory neurons located in the rostral ventrolateral medulla, and a direct input from the NTS to a group of vagal preganglionic neurons located in the ventrolateral portion of the nucleus ambiguus inducing baroreflex-mediated cardioinhibitory effects.

Furthermore, an additional continuous modulation of the baroreflex dependent on behavioral and physiologic conditions is responsible for the short- and long-term control of arterial blood pressure, including modulation of blood pressure variability.

Our studies showed that in OSA patients BRS is significantly impaired both during wake and different sleep stages and that reduced BRS is also associated to the development of excessive daytime sleepiness (Cortelli et al., 2012; Parati et al., 1997). Additionally, evidence is available that OSA-related reduction in BRS and increase in LF/HF ratio can be reversed after acute and prolonged CPAP treatment.(Bonsignore et al., 2002; Noda et al., 2007)

Similar findings have been reported by measuring plasma or urinary cathecolamines: Dimsdale and colleagues demonstrated for the first time that 24-hour urinary norepinephrine levels were higher in patients with OSA (Dimsdale et al., 1995) and recently our group confirmed that CPAP can correct the pathological sympathoadrenal activation in patients with OSA (Gilardini et al., 2018).

Other than CPAP, also the use of oral appliances is associated with the modulation of ANS: Coruzzi and colleagues demonstrated that in a cohort of OSA patients, 3 months of treatment with the oral device determined a reduction in apnea-hypopnea index ($p < 0.001$), a lengthening in R-R interval, an increased HF power (from 13 ± 26 to 502 ± 48 ms^2, $p < 0.001$), and a reduction in LF/HF RRI power ratio in HRV, consistent with an improvement in cardiac autonomic modulation (Coruzzi et al., 2006).

Interestingly, in a study comparing patients with bilateral carotid body tumor resection and a matched control group an impaired baroreflex function has been described in the form of reduced LF power of the heart rate variability spectrum in active wakefulness, sleep stage 1 and REM sleep. Conversely, sleep-related heart rate changes were similar in the two groups suggesting that the effects of sleep on heart rate are predominantly generated through central, non-baroreflex mediated pathways (Niemeijer et al., 2015).

Finally, withdrawal studies confirmed that when OSA treatment is discontinued there is a relapse of OSA symptoms but also of blood pressure surges and cathecolamine secretion (Kohler et al., 2011).

When considered all together, these findings suggest that a reduced BRS is a feature of OSA before the onset of cardiovascular complications and that the chronic hypertensive state associated with OSAS might be viewed as the result of ANS adaptation, together with excessive daytime sleepiness, to the episodic recurrence of sympathetic surges during the night.

3. Changes of ANS and corresponding non cardiovascular alterations in OSA

OSA is associated, as discussed before, with alterations of ANS involving the cardiovascular system, and leading to hyperactivation mainly of the sympathetic branch with increased heart rate and blood pressure surges. However, corresponding alterations have not been clearly demonstrated for other functions regulated by ANS (Fig. 1).

For instance, PNS and SNS interactively contribute to respectively constrict and dilate pupils: Philby and colleagues tried to demonstrate a dysfunction of this regulation in children with OSA but failed to show a difference when using pupillometric measurements (Philby et al., 2015). Interestingly they found a difference in terms of norepinephrine plasma levels (87.4 ± 14.7 vs 169.5 ± 29.6 pg/mL, $P < 0.01$) and blood pressure in children with severe OSA compared to habitual snorers suggesting the occurrence of ANS perturbations related to sleep disordered breathing in these subjects. Very few studies were conducted in adults: Micieli et al. (1995) showed only slight alterations of ocular ANS function, generally in the form of a reduced function of both sympathetic and parasympathetic branches. Although this study had some limitations like the small sample of subjects enrolled and the lack of a control group, the authors showed that pupillometry was more sensitive than cardiovascular indexes in detecting neurovegetative involvement correlated with respiratory indices.

Moreover, one of the main symptoms that patients with OSA complain of during consultations is mouth dryness. Xerostomia is common in many conditions however, and when not caused by a damage of the salivary glands, it can be due to an imbalance of ANS. To the best of our knowledge there is no study in the literature showing that dry mouth in OSA is caused by an ANS dysfunction, although reported by many patients with sleep disordered breathing.

Kirkness et al. (2005) showed that in patients with OSA there is an increase in the surface tension of the upper airway mucosal lining liquid without demonstrating an abnormal salivary flow rate. Several studies demonstrated an improvement in mouth dryness after OSA treatment (Avlonitou et al., 2012). However, it is difficult to discriminate whether this improvement was due to a recovery of ANS balance or rather to other causes such as better mouth hydration.

ANS regulates also the lower respiratory tract diameter, constricting and dilating bronchi with the parasympathetic nervous system being the dominant neuronal pathway in the control of airway smooth muscle tone. Interestingly, patients with OSA exhibit an increased vagal tone during each apneic event as a consequence of partial or complete

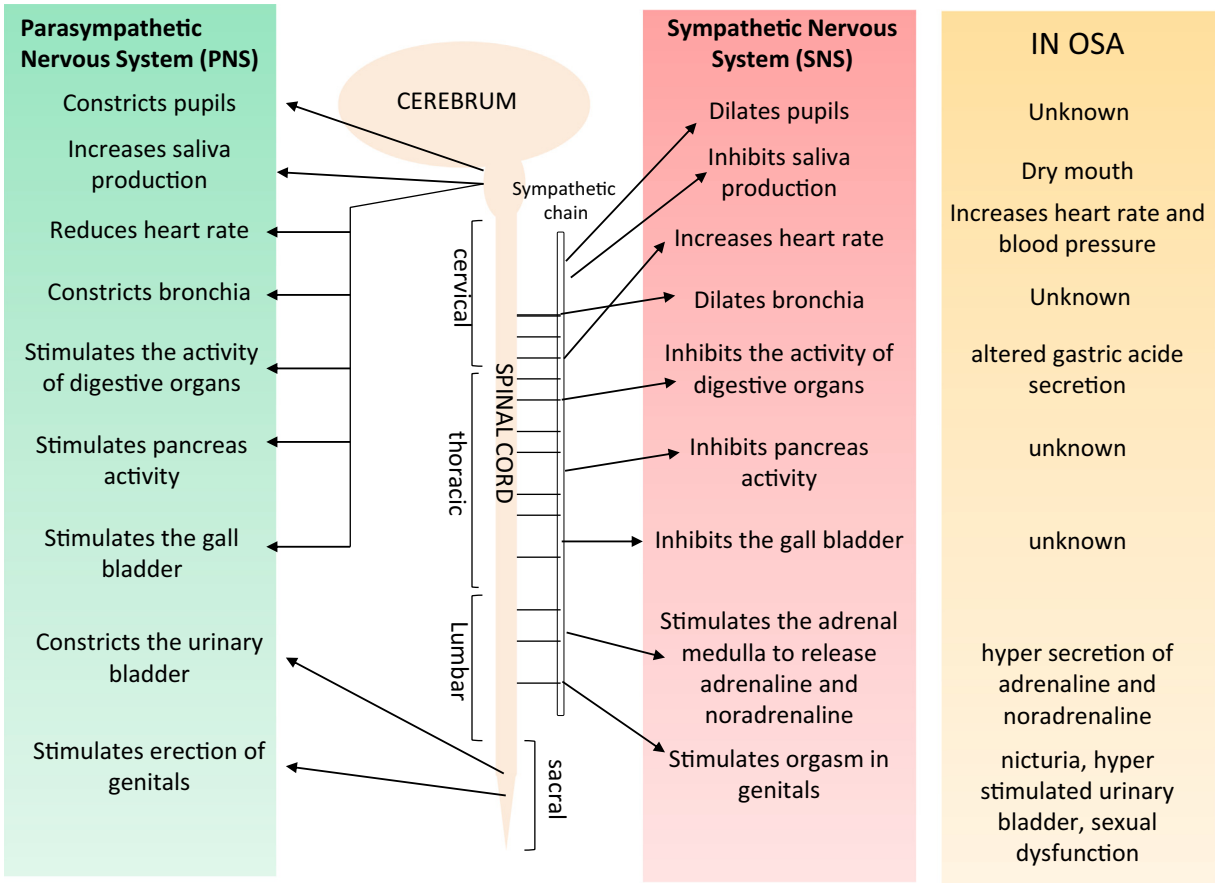

Fig. 1. Sympathetic and parasympathetic alterations in OSA.

airway obstruction, similar to what happens during Muller manoeuvre (Guilleminault et al., 1984). However, such imbalance of ANS seems to be limited to sleep apneas without any clear carry over effect during the daytime with regards to the lower respiratory tract diameter regulation.

Interestingly, patients with asthma have higher prevalence of OSA when compared with normal subjects (Alkhalil et al., 2008) suggesting a potential common underlining mechanism.

However, rather than a primary dysfunction of ANS as the main cause of bronchoconstriction in OSA it is likely that a chronic inflammation of both upper and lower airways plays an important role. In fact Wang et al. (2015) showed that in a cohort of patients with chronic obstructive pulmonary disease, those with OSA exhibited higher TNFα concentration and IL-8 levels measured on bronchoalveolar lavage fluid and that such alterations were reduced by CPAP treatment.

The ANS has a huge influence on gastrointestinal tract with particular emphasis on motility, secretion and modulation of gastrointestinal functions. SNS exerts a predominantly inhibitory effect upon gastrointestinal muscles and provides a tonic inhibitory influence over mucosal secretion while PNS exerts both excitatory and inhibitory control over gastric and intestinal tone and motility.

Patients with OSA might exhibit an altered secretion of gastric acid: a study in 63 OSA subjects matched for age, BMI, FEV1 and alcohol consumption showed that patients with OSA spent more time at pH 4 and had a greater number of acidic reflux events compared with control subjects (Ing et al., 2000).

However, many studies on the relationship between acid reflux and OSA did not account for obesity which is itself associated with increased sympathetic traffic. In fact, the coexistence of OSA and obesity makes it difficult to discriminate which ANS alterations are due to the former or the latter.

The bladder is controlled by the central nervous system. The bladder smooth muscles are controlled by ANS: PNS stimulates contraction of the detrusor muscle while SNS stimulates contraction of the internal urethral sphincter. In a nutshell: the parasympathetic branch inhibits urine storage and stimulates urination and SNS favours urine storage and inhibits urination.

In OSA a dysfunction of this balance has been demonstrated: Kemmer and colleagues showed that males with OSA had an overactive bladder with urgency incontinence when compared with patients with non OSA upper airway resistance syndrome serving as control. This relationship has been demonstrated also in women suggesting a role of the ANS dysfunction in the development of urinary symptoms in OSA (Lowenstein et al., 2008).

Much like control of the bladder, sexual responses are mediated by the coordinated activity of sympathetic, parasympathetic and somatic innervation. The relevant autonomic effects include: the mediation of vascular dilatation, stimulation of prostatic or vaginal secretions, smooth muscle contraction of the vas deferent during ejaculation or rhythmic vaginal contractions during orgasm in females, and contractions of the somatic pelvic muscles that accompany orgasm in both sexes.

Such functions are somewhat altered in patients with OSA: in a cross sectional analysis of 401 males undergoing polysomnography, erectile dysfunction was diagnosed through the validated 15-item International Index of Erectile Function questionnaire in 69% of patients assuming OSA diagnosis for an apnea hypopnea index (AHI) > 5 (Budweiser et al., 2009). The association between OSA and sexual dysfunction has been confirmed also for women (Subramanian et al., 2010).

Interestingly, some authors tried to evaluate whether treatment of OSA by means of continuous positive airway pressure (CPAP) was useful to reduce symptoms of erectile dysfunction: Pascual and co-authors randomised 75 patients with OSA to receive CPAP or no treatment

and found that, although sexual satisfaction was increased, CPAP use was not consistently associated with a net benefit on erectile function (Pascual et al., 2018).

4. Clinical implications of ANS dysregulations

From a clinical standpoint, the above described ANS alterations are obviously involved in the development of systemic arterial hypertension but also in the development of other clinical symptoms of OSA, such as excessive daytime sleepiness, which represent a challenge for sleep physicians because they are not easily predictable and are not often associated with OSA severity (et al., 2000). In fact, oxygen desaturations (Mediano et al., 2007) or sleep fragmentation (Guilleminault et al., 1988) could be referred to autonomic imbalance.

As the brainstem neurons play an important role in controlling sleep and vigilance, phasic and tonic autonomic changes induced by OSA might represent sensitive additional markers of the concomitant perturbation of sleep quality and, thus, of the occurrence of daytime sleepiness in patients with sleep disordered breathing (Puizillout and Foutz, 1977; Golanov et al., 2001).

This is the working hypothesis of a study we conducted in our lab which allowed us to demonstrate that patients with excessive daytime sleepiness (EDS), as objectively quantified by Multiple Sleep Latency Test, when compared with patients without, had lower baroreflex sensitivity and higher low-to-high frequency power ratio of heart rate variability (reflecting an enhanced sympathetic cardiac modulation) during the different sleep stages (Lombardi et al., 2008). Our data are also in line with previous experimental and clinical studies providing evidence of baroreceptor afferent influences on the level of vigilance during wakefulness. Moreover, baroreceptor afferent fibres also affect the catecholamine content of several cerebral areas, in particular the medulla and the posterior hypothalamus, which are implicated in the control of vigilance.

Thus, excessive daytime sleepiness could be interpreted as an allostatic response of central nervous system to SDB, probably reflecting autonomic arousals not detectable in the EEG.

However, similar studies in different cohort of patients could not replicate the same findings, thus suggesting that the way we assess daytime sleepiness (subjective vs objective), the general phenotype of patients and the presence of comorbidities could significantly affect the relationship between sleep apneas and EDS.

Interestingly, some studies highlighted also that excessive daytime sleepiness, assessed subjectively, can predict the development of hypertension, in a way supporting previous work suggesting an altered baroreflex sensitivity and heart rate variability in sleepy patients with OSA(Goldstein et al., 2004; Ren et al., 2016).

The role of ANS dysregulation might be important in the management of patients with hypertension: patients that exhibit enhanced sympathetic activation expressed with elevated heart rate at baseline are more likely to benefit from OSA treatment in terms of blood pressure reduction at follow-up (Pengo et al., 2014).

Thus, the presence of these autonomic alterations can be a useful tool to guide clinicians towards a more appropriate therapeutical approach for OSA-related hypertension.

Other than the hypertensive disease, ANS alterations do have an impact on the development of cardiac arrhythmias. In a canine model of OSA, direct neural recordings from ganglionated plexi, located at the junction of the aorta, superior vena cava and right pulmonary artery, revealed markedly increased neural activity preceding the initiation of AF. Furthermore, ablation of such ganglionated plexi markedly suppressed AF inducibility in this canine model of OSA (Ghias et al., 2009).

Lastly, ANS activity is altered in patients with heart failure and sleep apnea. When measured through heart rate variability assessment (Szollosi et al., 2007), an increased sympathetic dominance is observed in these patients. Different patterns of HRV in CSA and OSA have been observed suggesting different pathophysiological mechanisms involved in these two respiratory events.

This has been confirmed with invasive neural traffic measurements: Mansfield and colleagues demonstrated that, among patients with heart failure, total body and cardiac sympathetic nerve activity are elevated in CSA compared with OSA and that such ANS alterations but not apnea severity are related to heart failure (Mansfield et al., 2003).

What still deserves further investigation is the prognostic effect of ANS dysregulation in HF patients with sleep apnea: it is already known since the seventies that patients with heart failure exhibit an attenuated baroreflex mediated bradycardia in response to a drug-induced rise in systolic arterial pressure (Eckberg et al., 1971), indicating a deranged baroreflex cardiac modulation which is known to carry prognostic information in heart failure (Cohn et al., 1984; Osterziel et al., 1995).

5. Conclusion and perspectives

To conclude, a large amount of studies have demonstrated that patients with OSA are characterized by ANS alterations mainly of the sympathetic branch. However, the vast majority of studies have focussed on cardiovascular alterations, which are easier to measure, somewhat neglecting the other functions regulated by ANS. Consequently, it is difficult to conclude whether OSA determines a global dysfunction of ANS or perhaps only a partial dysfunction sparing in a way some vital functions such as bronchial dilatation/constriction or changes in the pupil diameter.

Furthermore, OSA related symptoms seem to be related to the degree of ANS dysfunction, whose indices may thus represent potential additional markers of the concomitant perturbation of sleep quality.

More evidence is therefore needed to better characterize the impact that sleep disorder breathing may have on ANS both in the short and long term.

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