

The sympathetic nervous system and catecholamines metabolism in obstructive sleep apnoea

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Abstract: Obstructive sleep apnoea (OSA) is the most common sleep disorder of breathing in middle-aged and overweight subjects. It features recurrent episodes of upper airway total (apnoea) or partial (hypopnea) collapse during sleep, which are associated with a reduction in blood oxygen saturation and with arousal from sleep to re-establish airway patency. An association of OSA with dysregulation of the autonomous nervous system (ANS) and altered catecholamines (CAs) metabolism has been contended for years. However, the pathophysiology mechanisms underlying these alterations remain to be fully clarified. Nonetheless, these alterations are deemed to play a key pathogenic role in the established association of OSA with several conditions besides arterial hypertension (HT), including coronary artery disease, stroke, and, more in general, with increased risk of cardiovascular (CV) events. Hence, in this review we will analyse the relationship between the sleep disturbances associated with OSA and the altered function of the ANS, including CAs metabolism.

Keywords: Obstructive sleep apnoea (OSA); sympathetic nervous system (SNS); catecholamines (CAs); cardiovascular risk (CV risk)

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Introduction

Obstructive sleep apnoea (OSA) is characterized by recurrent episodes of total (apnoea) or partial (hypopnea) upper airway collapse, which last ≥ 10 seconds and occur during sleep. They are usually associated with a reduction in blood oxygen saturation, respiratory effort, and arousals from sleep required to re-establish airway patency (1,2). The repetitive nature of these events during the night can lead to a prominent sleep fragmentation and to the development of typical signs and symptoms associated to OSA. These symptoms can be divided into those occurring during daytime (e.g., daytime sleepiness, morning headache, inability to concentrate, etc.) and those occurring during night time (e.g., snoring, choking or gasping during sleep,

restless sleep, nocturia). Moreover, OSA is associated with cardiovascular (CV) complications, such as arterial hypertension (HT), pulmonary HT, arrhythmias, stroke, as well as with diabetes mellitus and metabolic syndrome (2). Multiple mechanisms have been contended to explain how OSA can increase CV risk and other morbidity factors, among which a key role can be played by the activation of the sympathetic nervous system (SNS), with related altered metabolism of catecholamines (CAs).

The relevance of OSA and the importance of a better understanding of its mechanisms is emphasized by the fact that sleep-related breathing disorders are common in middle-aged, overweight men and women. Because of this, due to the on-going obesity epidemic, the prevalence of OSA is steadily on the rise (3): in the 1990's OSA involved 4% and

2% of middle-aged American men and women, respectively (4); current estimates are 10% and 3% of 30–49-year-old men and women, respectively (5,6). Therefore, aim of this review is to analyse the possible mechanisms by which OSA determines the dysregulation of autonomous nervous system (ANS), and thereby impact on CV risk.

Autonomous nervous system (ANS)

SNS and parasympathetic nervous system (PNS) interactively regulate visceral functions to maintain the body homeostatic milieu, and to enable reaction and adaptation to external and internal stressor stimuli (7,8). A very composite and intermingled mechanism operates at different levels, both centrally and peripherally, to coordinate the function of SNS and PNS. Under physiological conditions, a reciprocal activation of these two autonomic subsystems, the so-called “sympathovagal balance”, exists, which permits the activation of one branch, i.e., sympathetic outflow, alongside a withdrawal of the other, i.e., parasympathetic drive, and vice versa (9). However, it has been suggested that the co-activation of both is also possible, and could play a role in peculiar situations, such as chemoreceptor reflexes (i.e., during apnoea), exercise, and cold face immersion (10,11).

Catecholamines (CAs) production and metabolism

CAs are important neurotransmitters and hormones that play a fundamental role in the regulation of physiological processes, including one of most primordial reactions: the “fight or flight” response. Dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline) have positive inotropic, chronotropic, and dromotropic effects, leading to increased cardiac output, blood pressure (BP) and heart rate (HR). Moreover, they facilitate breathing by bronchodilation, and mobilize energy substrates from metabolic reserves by lipolysis and glycogenolysis.

The adrenal medulla and the post-ganglionic fibres of the SNS are the main sites of production, storage, and release of CAs. Synthesis of CAs relies on tyrosine, as a substrate, and involves activity of two enzymes, tyrosine hydroxylase (TH), and dopamine β -hydroxylase (DBH), which converts dopamine to norepinephrine (12) as showed in *Figure 1*.

A key step for controlling norepinephrine and epinephrine effects entails their inactivation to the inactive metabolites, normetanephrine and metanephrine, respectively, operated by the enzyme catechol-O-methyl

transferase (COMT). However, the latter also acts on others compounds with a catechol structure, as catecholestrogens and catechol-containing flavonoids. Hence, an altered activity of this enzyme can conceivably affect the bioactivity of all these substances.

COMT is coded by the COMT gene, located in the 22q11 region, which contains a non-synonymous single nucleotide polymorphism (rs4680G/A) that results in a valine (G allele) to methionine (A allele) mutation at position 158 (Val158Met) (13). This polymorphism was showed to imply different enzymatic activity: with the Val/Val carriers having a three-to-four-fold higher enzymatic activity than Met/Met carriers (14). Consequently, Met/Met women with a lower COMT activity showed higher oestrogen (estradiol) levels that could protect them from the development of HT and CV diseases (15). Notwithstanding this evidence, the role of altered COMT activity in OSA patients has never been investigated thus far, leaving unknown if it could affect the metabolism of CAs, and play a mechanistic role in HT and CV events.

How to measure the autonomic nervous system activity

Direct measurements

ANS activity can be measured directly or indirectly. Direct measurement of sympathetic nerve traffic in a given district can be accomplished with microneurography. This technique uses 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 $\text{M}\Omega$ at 1 kHz), which 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 and skin (muscle sympathetic nerve activity, MSNA, and skin sympathetic nerve activity, SSNA) provides information on the neural control of autonomic effector organs, including blood vessels and sweat glands. Accordingly, sympathetic microneurography represents a useful tool to investigate neural function and dysfunctions that involved BP control and body temperature regulation (16).

Moreover, the MSNA recording has been exploited to investigate changes in sympathetic neural traffic during sleep, and sleep-related events, such as sleep apnoea. These studies have shown that MSNA changes markedly during

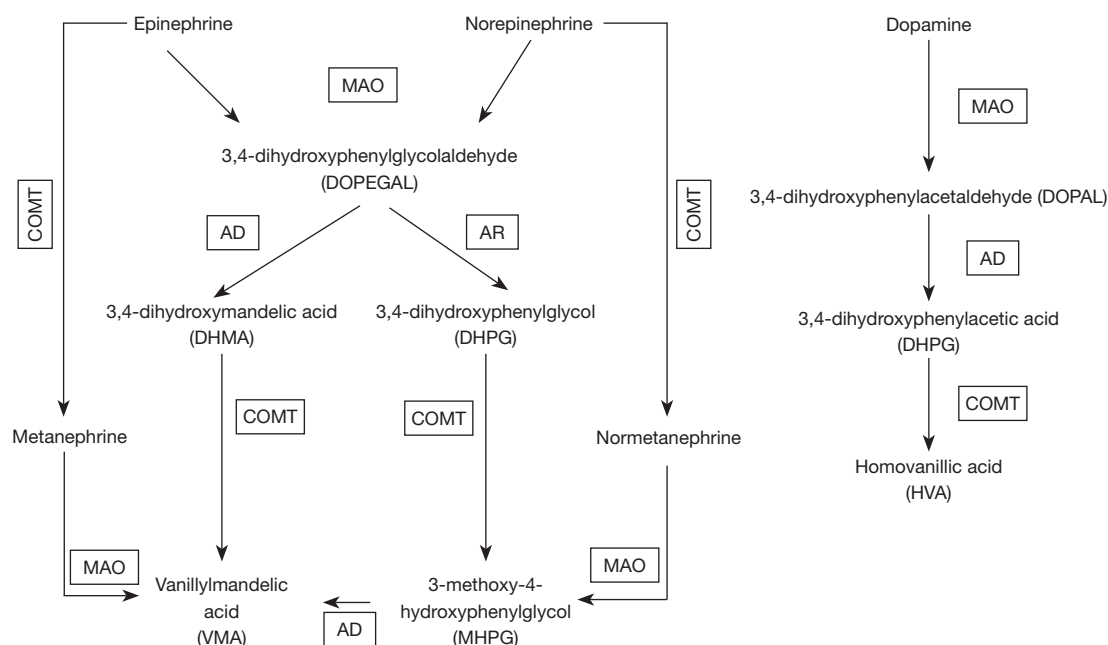


Figure 1 Catecholamines metabolism (12). MAO, monoamine oxidase; AD, aldehyde dehydrogenase; AR, aldehyde reductase; COMT, catechol-O-methyl transferase.

sleep: when the subject falls asleep MSNA decreases (17). Simultaneous sympathetic microneurography and polysomnographic recordings revealed that during supine sleep the reduction of burst rates of MSNA in the peroneal or tibial nerve was proportional to the depth of non-rapid eye movement (NREM) sleep. During rapid eye movement (REM) sleep the MSNA was almost as high as, or even higher than in the awake state (17). Of note, OSA patients with HT, who maintained a high MSNA level during NREM sleep, showed markedly elevated baseline MSNA, and less suppressed MSNA as compared to normal subjects (18,19). Unfortunately, the invasive and technically demanding nature of this technique prevented its widespread and regular use even in most clinical research settings.

Indirect measurements

Blood and urine CAs levels and their metabolic products

In 1995, Dimsdale *et al.* by measuring the plasma levels and urinary excretion of CAs in 43 hypertensive and normotensive individuals, with and without sleep apnoea, reported, for the first time, that 24-hour urinary norepinephrine levels were higher in patients with OSA

than in patients without OSA (58.2 *vs.* 40.2 ng, $P < 0.002$), both during the day and at night (20). We are going to analyse this indirect measurement in detail below in the text.

Power spectral analysis of heart rate variability (HRV)

HRV analysis entails a non-invasive reliable tool to assess the sympathetic and parasympathetic modulation, in physiological and pathological conditions (8,9,21). HRV depends on assessment of rhythmic oscillations embedded in heart period and BP time series, which reflect the sympathetic and parasympathetic modulations of CV function (22). The simplest method for analysing HRV is the calculation of the time domain measures, which can be derived from the analysis of the total electrocardiographic recording, or from shorter (but not shorter than 5 minutes) segments of the recording period. The most used time domain variables are: AVNN (ms) that represents the average of NN intervals for period of interest and can convert to average HR of NN intervals; the standard deviation of NN intervals-SDNN (ms)-that reflects total HRV; the standard deviation of AVNN for 5 minutes intervals for period of interest-SDANN (ms)-reflects primarily circadian HRV; the SDNN Index (ms), the average of 5 minutes standard deviations of NN intervals, represents the average of short-term HRV and combined

Table 1 Frequency domain measurements (21,22)

Variable	Description
TP over measured period (ms ²)	Reflects total HRV
ULF power (ms ²)	Measures rhythms greater than every 5 minutes and reflects circadian HRV
VLF (v.n. 0.0033-0.04 Hz) (ms ²)	Measures rhythms between every 25 seconds and every 5 minutes. Reflects vagal and renin-angiotensin-aldosterone system effects on HR
LF power (v.n. 0.04-0.15 Hz) (ms ²)	Reflect combination of SNS and PNS influences. Captures baroreflex rhythms
HF (v.n. 0.15-0.4 Hz) (ms ²)	Captures variations in HR due to respiratory sinus arrhythmia at 9–24 cycles/min. Under normal circumstances reflects vagal activity
LF/HF ratio	Reflects SNS/PNS balance
LFnu (%)	Reflects SNS activity
HFnu (%)	Reflect PNS influences activity

TP, total power; HRV, heart rate variability; ULF, ultra low frequency; VLF, very low frequency; HR, heart rate; LF, low frequency; SNS, sympathetic nervous system; PNS, parasympathetic nervous system; HF, high frequency.

SNS and PNS influences (21). Another method entails the frequency domain measures derived from the power spectral density (PSD), which provide information on how power (i.e., variance) distributes as a function of frequency (*Table 1*).

Variables derived from HRV analysis include the power of the high-frequency (HF) range (0.15–0.4 Hz), which reflects the parasympathetic modulation of the HR as sympathetic stimulation of the sinus node is substantially attenuated at frequencies above 0.15 Hz. At variance, the power of the low-frequency (LF) range reflects both sympathetic and parasympathetic activation. Accordingly, the LF/HF ratio is an estimation of the sympatho-vagal balance: an increased ratio indicates an enhanced sympathetic activity and/or a reduction of vagal activity. The physiological explanation of the very low-frequency (VLF) component is much less defined; it is considered a marker of hormonal and humoral fluctuations. VLF reflects underlying periodicities in HR at frequencies of every 25 seconds to every 5 minutes (0.0033–0.04 Hz). It involves the underlying frequency of most sleep-disordered breathing and periodic limb movements (PLMs). Limited data suggest that VLF can be modulated by a joint action of the renin-angiotensin-aldosterone system [since it was reduced by angiotensin converting enzyme (ACE) inhibition] and the PNS (since it was blocked by atropine), but not by the SNS since it was not affected by beta-blockade (22).

Peripheral arterial tonometry (PAT)

This technology involves a finger-mounted pneumo-optical sensor that measures continuously the arterial pulse

wave volume without the confounding effect of venous pulsations, which are eliminated. Episodes of upper airway obstruction cause vasoconstriction of digital vascular beds due to activation of the SNS, which results in attenuation of the PAT signal (23–25).

Sleep physiology and sympathetic nervous system (SNS)

The sleep process is characterized by the activation of a number of cortical, subcortical and medullar neural circuits, which cooperate in controlling sleep alongside hormonal changes (i.e., melatonin and orexin), local factors such as adenosine accumulation, circadian variations (i.e., dark-light cycles) and other unknown factors (26). A key role in the physiology of sleep is played by the ANS, which modulates CV functions during the onset of sleep and the transition to different sleep stages (27). Sleep stages classification depends on the observation of electroencephalographic waves and patterns, electro-oculographic patterns, and mental or submental muscle tone, as recorded by a full polysomnography. According to the American Academy of Sleep Medicine, the following terminology was recommended to separate the stage wakefulness (W) from the other two main, different sleep stages: NREM stages: N1, N2, and N3, and REM sleep. During normal sleep these stages progress cyclically from N1 through REM, then begin again with stage N1. A complete sleep cycle takes an average of 80 to 110 minutes with approximately 5 sleep cycles occurring in a normal night. The switch from W-to-sleep and among the different sleep stages is

not mono-directional (i.e., from NREM to REM, and vice versa). This mechanism could be associated with the occurrence of arousals (28,29). It is well known that sleep is involved in the regulation of function of peripheral organs. In healthy subjects, during sleep, there are physiological changes in ventilation, HR, and BP that are predominantly sleep-stage dependent, and are mediated by modifications in autonomic control (30).

NREM sleep

During NREM sleep stages, particularly during stage N3, there is a progressive reduction in central respiratory drive, minute ventilation, and arterial oxygen pressure (PaO_2), accompanied by a rise in arterial carbon dioxide pressure (PaCO_2). During this stage there is a simultaneous increase in parasympathetic tone alongside a decrease in sympathetic activity, with ensuing reduction in HR, BP and BP variability, stroke volume, and systemic vascular resistance. The lowering of HR seems to be mainly related to the increase in the parasympathetic activity, whereas the decrease in BP appears to be primarily related to a reduction in the sympathetic vasomotor tone (17). The physiological respiratory sinus arrhythmia observed during NREM sleep is due to a sinusoidal modulation of HR variation. During inspiration, in order to ensure adaptation to the increased venous return, HR accelerates, resulting in an increase in cardiac output; during expiration HR slows progressively (31).

REM sleep

During REM sleep the cardiac efferent vagal tone is suppressed (32), SNS is increased to levels similar to those in W stage with an increase of HR and BP. Atonia of the respiratory muscles, excluding the diaphragm, and a reduction in chemo-sensitivity both occur in REM stage, and the combination of these two factors results in an increase in PaCO_2 , and decrease in ventilation to levels lower than that seen in NREM sleep (17).

Arousals

Arousals from sleep are associated with abrupt increases in both respiratory and CV activity; the associated augmentation of ventilatory drive exceeds that expected for the given PaCO_2 level (33). At the same time, there is an increase in sympathetic activity and a decrease in cardiac

vagal activity exceeding normal W stage levels, causing significant surges in HR and BP (30).

Sympathetic nervous system (SNS) and obstructive sleep apnoea (OSA)

In combination with other co-factors, sympathetic and catecholaminergic alterations play a key role in the pathophysiology of the CV morbidity in adults with OSA. The repetitive episodes of complete or partial obstruction of the upper airway during sleep lead to several consequences in particular an increase in airway resistance and respiratory effort that may produce oxygen desaturation, hypercapnia, and central nervous system arousal to restore airflow. These different mechanisms are associated with alterations of the hemodynamic balance related to changes in the activity of ANS (26,34,35).

The physiological responses to obstructive apnoea are triggered mainly by the reduction of PaO_2 . During hypoxia, chemoreceptor activation (so called “oxygen-conserving reflex”) promotes hyperventilation to enhance oxygen delivery to blood. This is followed by an increase of SNS activity that mediates vasoconstriction to redistribute oxygenated blood flow to vital organs. At the same time PNS is activated with consequent bradycardia, in order to reduce myocardial oxygen demand (17,36-38). Once normal breathing resumes, venous return and cardiac output increases. But the increase of the latter occurs into a highly constricted peripheral vasculature, which determines an increase of BP at the end of each apnoea. When the enhanced sympatho-excitation is sustained over years, as is the case in OSA patients, this physiologic response becomes pathological and can be responsible of the “non-dipping” BP profile at night, which, by itself, has been associated with an increased CV risk (30).

The respiratory and autonomic changes that occur during each acute obstructive apnoea episode are summarized in *Figure 2*.

Other consequences of OSA are:

- Peripheral vasoconstriction, due to activation of the ANS, with consequent increase of peripheral resistance. This phenomenon persists for several seconds after ventilation resumption, due to the kinetics of norepinephrine uptake, release, and washout at the neurovascular junctions (44).
- Increase of the left ventricular transmural pressures, causing increased of the left ventricular afterload secondary to the augmented negative inspiratory intra-

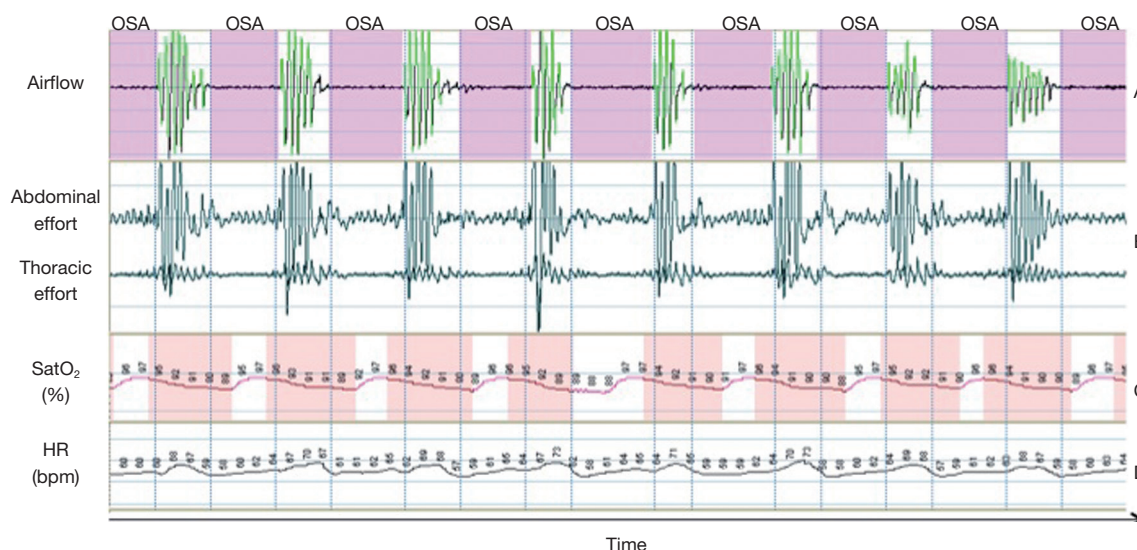


Figure 2 Respiratory and autonomic changes during acute OSA. (A) Airflow trace; (B) thoracic and abdominal efforts traces. BP decreases during the initial part of the apnoea and rises when SpO_2 decreases at the end of the apnoeic event. When the ventilation resumes, HR and BP reach a peak (39). The increase in BP occurring during ventilation resumption may elicit a reduction in the ventilatory and sympathetic responses to chemoreflex stimulation by hypoxemia (40,41). Moreover during an apnoea, the lung inflation reflex may not occur, and this may contribute to an increase in ANS (42). In contrast, the reflex may be exacerbated during ventilation resumption, when ANS is abruptly inhibited; (C) oxygen saturation. Hypoxemia stimulates arterial chemoreceptors and causes an increase in efferent ANS (38). Hypercapnia may induce a higher ventilation, HR, cardiac output and BP (43); (D) heart rate trace. HR can slow down, increase or remain unchanged, depending on whether parasympathetic or sympathetic influences predominate (33). OSA, obstructive sleep apnoea; BP, blood pressure; HR, heart rate; ANS, autonomous nervous system.

thoracic pressures generated against the occluded upper airway. These changes also increase venous return, and right ventricular pre-load, whilst OSA-induced hypoxia results in pulmonary vasoconstriction, leading to increases in right ventricular afterload. Collectively, right ventricular distension, impairment of left ventricular filling, and increased sympathetic activity increase myocardial oxygen demand in a setting in which apnoea-related hypoxia reduce tissue oxygen delivery (45).

As mentioned before, HRV represents an indirect measure of ANS activity. Sleep is the ideal condition to measure ANS activity, as it is not influenced by other conditions, such as physical activity and higher cortical function. The interaction between ANS and sleep is complex, bidirectional and regulated by several different factors. Changes in ANS regulation can profoundly affect sleep onset and sleep homeostasis; on the other hand, modifications of physiological sleep can influence the autonomic CV regulation. During sleep, autonomic cardiac control fluctuates between sympathetic and parasympathetic

predominance, mainly depending on the transition to different stages (*Figure 3*). According to Somers *et al.* the CV system would be strongly affected by sleep stages in that W, NREM and REM sleep are related to a different haemodynamic status (17).

HR and BP variability are altered in patients with OSA, even in the absence of HT, heart failure, or other CV diseases. More importantly the degree of derangement in CV variability may be linked to the severity of OSA and, therefore, can represent a potential marker of sleep disorder breathing (18). Compared to controls, patients with OSA are characterized by a possible shift of the sympatho-vagal balance toward a sympathetic predominance and a vagal withdrawal, as shown by the increase of LF component and LF/HF, and the reduction of the HF component, either during night time or wake (30). This abnormal HRV pattern in patients with OSA has been confirmed in many studies although other authors could not replicate the same finding (*Table 2*). This is probably due to the different methods used to analyse HRV (fast Fourier transform, autoregressive method, coarse-graining spectral analysis), which limit the

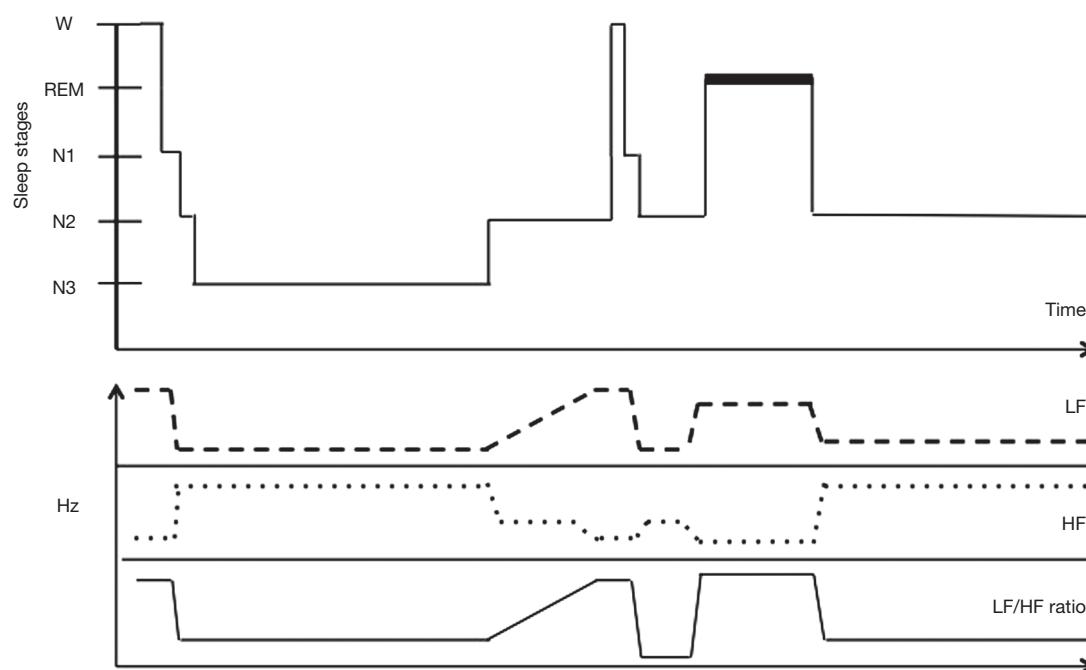


Figure 3 Normal hypnogram (fragment)-frequency domain variables modifications during normal sleep. In normal subjects the transition from W to N1 is characterized by an increase of HF component (parasympathetic activation) and decrease of LF, which determines a decrease of LF/HF ratio. From N1 to N3, the stage of highest neural synchronization, an additional gradual decrease is observed in HR, with minimum values reached during N3, also called “deep sleep”. During REM stage LF values do not change significantly but the HF component decreases reaching the levels observed during the W; so the transition from NREM to REM is accompanied by an increase of HR (42). HF, high-frequency; LF, low-frequency; HR, heart rate; REM, rapid eye movement; NREM, non-rapid eye movement.

ability to compare adequately different studies.

Other studies have showed the benefits of continuous positive airway pressure (CPAP) therapy on HRV (53-55), even after one night of treatment (56). CPAP is the gold standard therapy for moderate to severe OSA (57); long-term CPAP treatment can reduce the sympatho-vagal imbalance, mostly in patients with moderate and severe OSA, both during REM and NREM sleep (47).

Other alternative treatments for OSA have shown a similar beneficial effect on HRV modulation. Choi *et al.* (58) evaluated the effect of upper airway (UA) surgery on HRV using frequency domain analysis for patients who have had either successful (n=22) or unsuccessful (n=14) surgery. They described significant changes in the former group, and, in particular a significant reduction of VLF power and LF power. However, HF power and LF/HF ratio did not change significantly after UA surgery. Enhanced sympathetic activity in subjects with OSA has been observed even during W, in conditions of stationarity (normal breathing and normoxia). In a recent study, comparing patients with

severe OSA (AHI ≥ 30), with and without heart failure, who were split into two subgroups according to the presence or absence of daytime sleepiness-measured through the Epworth Sleepiness Scale (ESS) questionnaire-subjects without excessive daytime sleepiness (EDS) had higher harmonic VLF power than patients with EDS. The ESS scores correlated inversely with VLF power in all subjects ($r=-0.294$, $P=0.005$) and in heart failure subjects ($r=-0.468$, $P=0.016$), which led the authors to conclude that in patients with heart failure, VLF harmonic power during sleep could be a more reliable index of sympathetic modulation of HR than the usual indices such as LF/HF and LF power. OSA appeared to be a stimulus potent enough to entrain sympathetic discharge in the VLF range of the apnoea-hypernea cycle (59).

Studies in humans have shown increased muscle sympathetic nerve activity (MSNA) under hypoxic conditions at simulated altitudes, which persisted even after removal of acute short-term exposure to intermittent hypoxia (60-63). Therefore, night time chronic intermittent

Table 2 Summary of selected studies investigating the clinical value of HRV in OSA patients

Authors	Study design	N	Participants	Age range	HRV Analysis	Results
Kim <i>et al.</i> , 2015 (46)	Retrospective analysis	164	83 with OSA (AHI >15/h), 81 controls	20–59 y (M)	Time and frequency domain variables	Some parameters of HRV, such as SDNN, and SDNN Index, in the time domain, were increased in OSA patients. In the frequency domain TP, VLF, LF, and LF/HF (P=0.015) were significantly higher in OSA group
Palma <i>et al.</i> , 2015 (47)	Prospective study	50	16 with moderate OSA (mOSA), 14 with severe OSA (sOSA), 20 controls	30–75 y (M + F)	Frequency domain parameters	sOSA exhibited higher LF power during NREM; both mOSA and sOSA exhibited significantly higher LF modulations during REM, lower HF modulations and higher LF/HF ratio, both during NREM and REM
Gammoudi <i>et al.</i> , 2015 (48)	Retrospective cohort study	30	16 with mild-to-moderate OSA, 14 with severe OSA	18–60 y (M)	Time and frequency domain variables	No significant difference have been observed in the severe OSA group except for the mean RR, which increased significantly during NREM sleep compared to the W. Compared to mild/moderate group, the high AHI group showed a significantly higher LFnu and LF/HF, and significantly lowers HFnu and HF, during S2
Palma <i>et al.</i> , 2014 (49)	Observational study	106	33 with OSA without hypoxia (–h), 37 patients with OSA with hypoxia (+h), 36 control subjects	35–75 y (only 15 females)	Time and frequency domain variables	The mean RR interval was similar in OSA – h, OSA + h and controls in all sleep stages, except in W-post, where RR interval was significantly lower in OSA + h. No significant differences were observed in the SDNN. The LF power and LF/HF ratio increased significantly in OSA + h during N1–N2 and REM when compared to OSA – h and controls. The HF in both OSA – h and OSA + h patients was significantly lower than in controls in N1–N2 and REM, but not during W-pre and W-post
Trimer <i>et al.</i> , 2014 (50)	Single-centre, cross-sectional, retrospective study	58	20 with mild OSA, 20 with moderate OSA 18 controls	>18 y (M + F)	Frequency domain variables	Controls presented higher values for both LF and LF/HF in REM sleep compared to N2 sleep, while the mild OSA group did not demonstrate the same autonomic behaviour between these sleep stages. Moderate OSA patients also presented higher values for both LF and LF/HF in REM sleep when compared with N2 and REM sleep of controls
Zhu <i>et al.</i> , 2012 (51)	Prospective study	46	23 with severe OSA, 23 controls	Mean age 45 y (M)	Time and frequency domain variables	OSA group had shorter mean NN whereas the 2 groups had similar SDNN, pNN50, and rMSSD. The frequency domain indices were similar
Lado <i>et al.</i> , 2012 (52)	Prospective study	46	20 with severe OSA, 10 with mild-moderate OSA, 16 controls	27–78 y (M + F)	Frequency domain variables	Results yielded significant differences for all the spectral components, with the sole exception of the LF in patients suffering mild OSA in the BORDERLINE and APNEIC intervals

HRV, heart rate variability; OSA, obstructive sleep apnoea; TP, total power; VLF, very low-frequency; LF, low-frequency; HF, high-frequency; REM, rapid eye movement; NREM, non-rapid eye movement.

hypoxia might contribute to the activation of the central nervous system and to the increase in peripheral chemosensitivity that are carried over into wakefulness, resulting in sustained daytime sympathetic overactivity (64).

The mechanisms involved in this phenomenon are:

- (I) Sustained elevation in CAs levels with down regulation of vascular sympatho-adrenergic receptors: a reduced response to the intra-arterial infusion of α - and β -receptor agonists was observed in OSA patients when compared to normotensive subjects (65);
- (II) Polymorphisms in α - and β -adrenergic receptor genes: the Arg389Gly polymorphism of the β 1-adrenergic receptor has been associated with an increased risk of OSA development in hypertensive men. Furthermore, occurrence of HT increased in subjects with mild OSA with increasing number of Arg389 alleles. A lack of an association has been reported between polymorphisms of the β 2-adrenergic receptor gene and OSA and between α -adrenergic receptor genes and OSA (66);
- (III) Cardiac vagal dysfunction: cardiac vagal regulation is comprised of a tonic and a dynamic component, which can be assessed by spectral analysis of HRV (22);
- (IV) Baroreflex changes: the baroreflex sensitivity is reduced during sleep and W in OSA patients compared to control subjects (67). In patients with refractory HT and OSA a single night of CPAP treatment was found to be associated with an increase in baroreflex sensitivity and decrease in systolic BP (68).

Over the years some studies have shown the presence of elevated levels of CAs in both urine and plasma suggesting increased sympathetic activity in patients with OSA. Moreover treatment with CPAP and other therapies, such as tracheostomy, lowered CAs levels (45,69-73). Elmasry *et al.* showed that, in a population-based sample of hypertensive males (n=116), OSA was associated with significantly increased urinary excretion of normetanephrine and metanephrine, when compared to non-OSA subjects. This association was independent of major confounding factors (age, BMI and severity of HT) (74). More recently Kohler *et al.*, in 102 males with moderate-to-severe OSA, randomised to therapeutic (n=51) or sub-therapeutic (n=51) CPAP treatment, showed that 4 weeks of therapeutic CPAP induced a significant reduction in urine normetanephrine excretion (179.7 ± 80.1 to 132.7 ± 46.5 $\mu\text{mol} \cdot \text{mol}^{-1}$ creatinine) which did not occur in the sub-therapeutic

group (75).

However, data from other studies and clinical trials have revealed a substantial variability regarding the effect of CPAP treatment on CAs levels and BP: some researchers reported a reduction in circulating CAs that extended into daytime and wakefulness (70,75), while others could not confirm a significant difference between treated and untreated OSA patients (76). Comondore *et al.* analysed 24-h urinary extraction of CAs, microalbumin, creatinine ratio, 24-h BP profile, and endothelial function markers in two groups of patients with AHI >15/h either treated with CPAP therapy or untreated. Patients treated with CPAP showed a trend to improvement of all these parameters, which, however, did not reach statistical significance ($P>0.10$) (77). These contrasting results can be explained by the fact that the therapeutic effect of CPAP on BP and sympathetic outflow is more prominent in hypertensive than in normotensive OSA patients, as showed by Heitmann *et al.* (78), who assessed the effect of CPAP therapy on norepinephrine kinetic. They found that in OSA patients CPAP treatment leads to a reduction in renal sympathetic neural activity by enhancing the renal clearance of norepinephrine rather than by attenuating norepinephrine synthesis rates. Kohler *et al.* have also showed that CPAP withdrawal was accompanied by elevation in urinary CAs (79). Thus, all these studies support the assumption that OSA patients are characterised by elevations in CAs levels that are attenuated by treatment.

Conclusions

OSA affects sympatho-vagal modulation, both during sleep and wakefulness. Although the underlying mechanisms are complex and involve both branches of the ANS, OSA-induced ANS changes may represent a key pathophysiologic link between OSA, HT and CV disease. Furthermore, in OSA patients with HT, CPAP treatment might reduce BP and CV events through a modulation of the ANS activity, but more studies are necessary to fully understand the mechanisms that cause CV damage in OSA patients and, most of all, whether measuring ANS imbalance can help understanding which OSA patients are more at high risk of developing arterial HT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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