This review focuses on the complex integration between cardiovascular reflexes and central autonomic influences controlling physiological sleep-dependent changes in arterial blood pressure and heart rate. A brief introduction on the anatomic and functional organization of the arterial baroreflex and the methods available to assess its function in humans is followed by an analysis of the functional interaction between autonomic nervous system and sleep mechanisms at the highest levels of brain organization. An insight into these interactions is important to shed light on the physiopathology of the most frequent complications of obstructive sleep apnea syndrome, such as sustained arterial hypertension, and excessive daytime sleepiness.

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arch and are innervated by the glossopharyngeal and the vagus nerves. They respond to changes in carotid or aortic stretch elicited by rises or falls in arterial pressure. Primary baroreceptor afferents provide monosynaptic excitatory input to the nucleus of the solitary tract (NTS). The NTS, the first central relay of baroreflex influences, is characterized by two autonomic efferent pathways: (1) a sym-pathoinhibitory pathway involving a projection from the NTS to inter-neurons in the caudal ventrolateral medulla which send an inhibitory projection to sympathoexcitatory neurons located in the rostral ventrolateral medulla, and (2) a direct input from the NTS to a group of vagal preganglionic neurons located in the ventrolateral portion of the nucleus ambiguous inducing baroreflex-cardioinhibitory effects. Via the NTS, the baroreflex also suppresses the secretion of vasopres-sin by magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus by inhibiting noradrenergic cells of the A1 group (Benarroch, 2008).

1.2. “Central” interaction on the baroreflex arc

There is also a “central” continuous modulation of the baroreflex dependent on behavioral and physiologic conditions. This baroreflex modulation contributes to both the short- and long-term control of arterial blood pressure (Di Rienzo et al., 2009), including the changes in blood pressure (BP) between daytime activities and night-time sleep, known as the BP “dipping” profile. The baroreflex is also involved in centrally mediated cardiovascular modulation, which may result in clinically relevant events such as emotional syncope and white coat hypertension.

Neural “top-down” inputs stemming from brain structures and directed to lower targets are classically referred to as “central control” mechanisms, originally termed “cortical irradiation,” a feed-forward mechanism able to induce marked stereotyped changes in autonomic, respiratory and motor responses during, for example, exercise, defensive behaviour, and psychological stress (Ruggiero et al., 1987; Yasui et al., 1991; Oppenheimer et al., 1992; King et al., 1999; Nowak et al., 1999; Williamson et al., 1999, 2001, 2002; Critchley et al., 2000).

Central command appears to modulate the sensitivity of the arterial baroreflex control of heart rate and BP (Mancia et al., 1982; Potts et al., 1993; Gallagher et al., 2001; Ogho et al., 2002; Michelinei, 2007) through inputs stemming from the hypothalamus, amygdala and parabrachial nucleus and directed to the NTS, which in turn has a bottom-up modulatory role exerting a generalized inhibiting effect by means of its ascending projections to the upper brain, influencing the activity of the periaqueductal gray, amygdala and hypothalamus either directly or via the parabrachial nucleus (Benarroch, 2008; Raven, 2008).

This reciprocal interaction between the hypothalamus and the NTS suggests that changes in baroreflex afferent activity may not only drive the moment-to-moment feedback regulation of BP and HR, but may also influence the higher level of the autonomic control, including the mechanisms adjusting the sleep–wake cycle (Benarroch, 2008).

2. Methods of assessing baroreflex function

Given the important role of the arterial baroreflex in neural cardiovascular regulation, and its complex interactions with other central and reflex control mechanisms, proper consideration should be given to the several methods proposed to assess the actual contribution of the arterial baroreflex to cardiovascular homeostasis.

The baroreflex response in humans is mostly evaluated by fitting blood pressure and heart rate recorded on a beat by beat basis to a sigmoid logistic function proposed by Kent et al. in 1972 (Parati et al., 2000; La Rovere et al., 2008). Several experimental techniques have used this method to evaluate arterial baroreflex function in animals, but these techniques are not applicable in humans. Hence, cardiovascular baroreflex sensitivity in humans has primarily been assessed by indirect methods (Parati et al., 2000). These indirect techniques include the assessment of reflex BP and/or HR changes related to changes in carotid transmural pressure induced by a neck chamber device; reflex changes in muscle sympathetic nerve activity and/or HR in response to BP changes induced by intravenous injection of vasoactive drugs; reflex changes in HR following spontaneous BP changes either in the time domain (sequence technique) or in the frequency domain. In particular, the slope of the reflex HR changes in response to BP changes is commonly referred to as baroreflex sensitivity (BRS) and quantified in msec/mmHg.

The advantages and limitations of the various indirect techniques available were reviewed by Parati et al. (2000). Due to the many papers showing its pathophysiological and clinical relevance, BRS is currently considered a useful comprehensive index of neural regulation of the sinoatrial node. BRS has a prognostic value in cardiovascular diseases like myocardial infarction and heart failure, and is impaired in pathological conditions ranging from neurological diseases to metabolic disorders (Skrapari et al., 2006).

Among the methods available to assess baroreflex sensitivity both in humans and in animals, those exploring baroreflex modulation of the cardiovascular system can be divided into methods assessing baroreflex modulation of efferent sympathetic activity, and methods exploring cardiac vagal modulation. Baroreflex modulation of sympathetic efferent influences in humans can be assessed by directly measuring changes in muscle sympathetic activity following BP changes induced by venous injection of phenylephrine or nitroprusside, or by estimating the changes in muscle sympathetic activity associated with spontaneous changes in BP. However, it should be emphasized that a dissociation between sympathetic and cardiac baroreflex function is often noted in conditions associated with elevated cardiovascular risk (Mancia et al., 1978; Grassi et al., 1998).

3. Baroreflex function during normal sleep

Several studies have shown that baroreflex function is state-dependent, meaning that it is differently modulated by central influences in the different sleep phases and by wake adaptive behaviours (Silvani, 2008).

Sleep is not a uniform condition. On the basis of polygraphic recordings, sleep has been divided into two different states: non-rapid eye movement sleep (NREMS), comprising four stages, and rapid eye movement sleep (REMS). In addition, NREMS is characterized by a complex microstructure defined by EEG markers including K-complexes, arousals and a cyclic alternating pattern (CAP), whereas the microstructure of REMS consists of tonic (i.e., low amplitude and desynchronized EEG activity, chin atonia) and phasic events (rapid eyes movements, bursts of muscular activity.

Sleep has a significantly more important and complex impact on physiological regulation than quiet and restful wakefulness. This is clearly shown by the physiological changes in motor control, BP, HR and respiratory activity documented during sleep in healthy controls. These changes suggest that autonomic functions are progressively modulated during NREM sleep, with a reduction in sympathetic and an increase in parasympathetic cardiovascular regulation. Conversely, irregular activation and deactivation of these functions occur during REM sleep (Halasz et al., 2004; Harris, 2005).

However, the cardiovascular changes occurring during sleep cannot be explained solely in terms of cardiovascular reflexes. Sleep-dependent tonic or phasic changes in BP, which can be quantified in a clinical setting using 24 h ambulatory BP monitoring techniques (Mancia et al., 1993), may result from the complex integration between the cardiovascular reflexes and central autonomic influences specific to each sleep state (Silvani, 2008). Convincing experimental evidence supports the conclusion that central autonomic influences directed to the heart and resistance vessels underlie the phasic
increases in ambulatory BP observed at the time of arousals and associated with K-complexes during NREMS. However, heart period values during NREMS are positively correlated with the concomitant and preceding values of ambulatory BP, suggesting a baroreflex-driven coupling between BP and R-R interval changes exerting a stronger influence in NREMS than in REMS and wakefulness both in animal models (lambs, rats) and humans (Parati et al., 1988; Silvani, 2008).

The main cardiovascular changes occurring during sleep in normal subjects are presented in Table 1; the autonomic changes during sleep in normal subjects compared with those occurring in patients with sleep-related breathing disorders are summarized in Table 2. To date, little is known about the relative contribution of central and reflex neural mechanisms to the observed sleep-specific complex changes in cardiovascular parameters. Indeed, cardiovascular physiology in sleep remains an open and active field of investigation where more research is needed (Parati, 2000).

### 4. Baroreflex function and obstructive sleep apnea syndrome

The obstructive sleep apnea syndrome (OSAS) with a continuous repetition of obstructive events during the night is a paradigm of how a sleep breathing disorder can lead to a permanent dysregulation of the autonomic cardiovascular control resulting in sympathetic overactivity. Indeed, an increase in sympathetic tone is thought to underlie the cardiovascular complications responsible for the increased risk of mortality in patients with sleep apnea (Bague et al., 2006; Friedman and Logan, 2009).

In this setting, assessment of "spontaneous" baroreflex sensitivity by the sequence method disclosed a clear-cut impairment of baroreflex control of HR, most prominent during NREM sleep in OSAS patients (Parati et al., 1997; Bonsignore et al., 2002, 2006; Lombardi et al., 2008). Conversely, a study on normotensive patients with OSAS has shown a selective impairment of the sympathetic response to baroreceptor stimulation, apparently not accompanied by any impairment of baroreflex HR control (Narkiewicz et al., 1998). The discrepancy between these results may depend on the methodology used to quantify baroreflex control of HR.

Intermittent hypoxia and changes in the mechanics of ventilation, together with arousal due to the activation of cortical and subcortical structures, have been implicated as important determinants of increased sympathetic activity in OSAS patients, although this topic remains a matter of debate.

Whatever the pathological mechanisms responsible, several large studies controlling for confounders have clearly established that OSAS is a risk factor for hypertension and cardiovascular disease including stroke (Pack and Gislason, 2009), and the autonomic and hemodynamic changes occurring in this condition play an important pathophysiological role (Parati et al., 2007).

The first study aiming to identify markers of the development of future daytime hypertension in a group of OSAS patients still normotensive during the day at baseline showed that a reduced baroreflex sensitivity and a hyperactive chemoreflex were characteristic features of OSAS in the awake state. This peculiar combination of reduced baroreflex and hyperactive chemoreflex function suggested that a central remodelling of autonomic cardiovascular control may precede the development of daytime hypertension (Cortelli et al., 1994).

Chronic intermittent hypoxia associated with recurrent apneas exerts two major effects on the carotid body including sensitization of the hypoxic sensory response and induction of sensory long-term facilitation. Studies on humans and experimental models suggest that alterations in acute O2 sensing by the carotid bodies, and hyperactivity of adrenal medullary chromaffin cells both contribute to the autonomic comorbidities associated with chronic intermittent hypoxia (Prabhakar et al., 2007) by activating specific inducible factors (hypoxia-inducible factors (HIFs), c-fos, nuclear factor of activated T-cells (NFAT), and nuclear factor κB (NF-κB)) and alterations in gene expression associated with increased oxidative stress (Prabhakar et al., 2009).

Moreover, the preliminary results (Cortelli et al., 1994) were subsequently confirmed by different methods of BRS computation, also showing that the reduced BRS of OSAS patients is independent of hypertension, obesity and age (Carlson et al., 1996; Narkiewicz et al., 1998). These conclusions are also in line with the autonomic data obtained during sleep evaluating BRS with the sequence technique. These studies showed that BRS was also depressed in OSAS during sleep, particularly stage 2 of NREM sleep, and that this alteration was reversed by OSAS treatment with CPAP (Parati et al., 1997; Bonsignore et al., 2002).

Thus a reduced BRS is a feature of OSAS before the onset of cardiovascular complications. This could be better understood from an allostatic perspective where the chronic hypertensive state associated with OSAS might be viewed as the result of autonomic nervous system (ANS) adaptation to the episodic recurrence of sympathetic surges during the night. Therefore, the reduced BRS consistently described in OSAS could be an indirect index of an as yet unknown maladaptive

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### Table 1

**Normal sleep-dependent changes of arterial blood pressure in humans.**

<table>
<thead>
<tr>
<th>NREMS</th>
<th>REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP variability</td>
<td>Increased from wakefulness</td>
</tr>
<tr>
<td>ABP mean</td>
<td>Increase due to changes in HR and constriction or dilation of different vascular beds</td>
</tr>
<tr>
<td>Arterial baroreflex</td>
<td>Cardiac baroreflex gain may be increased, unchanged or decreased with respect of NREM</td>
</tr>
<tr>
<td>Spontaneous fluctuations of ABP and HR</td>
<td>Changes in ABP result from central autonomic command and are not invariably accompanied by changes in HR</td>
</tr>
<tr>
<td>Prevalent pattern of &quot;hypertension and cardiac slowing&quot; (baroreflex control) stronger than in wakefulness; Pattern of &quot;hypertension and tachycardia&quot; (central control) do occur but mainly in association with arousals</td>
<td></td>
</tr>
<tr>
<td>Pattern of &quot;hypertension and cardiac slowing&quot; (baroreflex control) does occur but with a weaker correlation than in NREMS</td>
<td></td>
</tr>
</tbody>
</table>

ABP = arterial blood pressure; NREMS = non-rapid-eye movement sleep; REMS = rapid-eye movement sleep; HR = heart rate.

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### Table 2

**Autonomic changes during sleep in normal sleep and in obstructive sleep apnea.**

<table>
<thead>
<tr>
<th></th>
<th>Parasympathetic tone</th>
<th>Sympathetic tone</th>
<th>BRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NREMS light (S1 and S2)</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>NREMS deep (S3 and S4)</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>REMS tonic</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>REMS phasic</td>
<td>↓↑</td>
<td>↑↓</td>
<td>↓↑</td>
</tr>
<tr>
<td>NREMS</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>OSA</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

NREMS = non-rapid-eye movement sleep; REMS = rapid-eye movement sleep; OSA = obstructive sleep apnea; direction of arrow indicates increase (up) or decrease (down); 2 arrows in the same direction indicate stronger autonomic effect; 2 arrows in the opposite direction indicate both increase or decrease of the autonomic function.

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mechanism. We can speculate that sympathetic activation, functional to the characteristic respiratory and cardiovascular effects of OSAS, when repeated over a long period of time in predisposed subjects, may change the afferent regulation of the barosensitive NTS neurons. This could attenuate their inhibitory effect on the sympathoexcitatory neurons of the rostral ventrolateral medulla which could in turn be responsible for the sustained chronic peripheral sympathetic overactivation and the resulting BP rise and increased cardiovascular risk.

According to this hypothesis, such an altered function of the barosensitive NTS neurons, may also have a bottom-up effect on the central autonomic regulation of the sleep–wake cycle. However, none of the markers of oxygen desaturation and sleep disruption were found correlated with excessive daytime somnolence (EDS), a disabling chronic complication of OSAS. For this reason, we explored whether the occurrence of EDS in untreated subjects with sleep-related breathing disorders (SRBD) of different severity might be related to other indices of autonomic activity such as an impaired cardiac autonomic modulation.

We evaluated 53 patients with SRBD who underwent nocturnal polysomnography (PSG) [Lombardi et al., 2008]; EDS was diagnosed objectively by the multiple sleep latency test. BRS was measured by sequence technique and cardiac sympatho/vagal balance by power spectral analysis of whole night ECG and continuous BP recording and separately over each sleep phase. The PSG indices of SRBD severity and quality of sleep were computed and correlated with the autonomic cardiac indices. Patients without EDS (nEDS group) and patients with EDS (EDS group) were matched for age, BMI, resting BP value and habitual consumption of alcohol, caffeine and nicotine, and no significant differences were found in sleep quality or sleep structure between the nEDS and EDS groups. In addition night-time values of BP and HR and lowest oxygen saturation were similar in both groups.

Hence, this study also failed to explain EDS by any of these variables. However, when we analyzed the baroreflex sensitivity and the cardiac sympatho/vagal balance, we found that patients with EDS had a reduced BRS and an increased LF/HF, which is believed to be a marker of sympathetic activity. Moreover, the impaired modulation of BRS and the LF/HF ratio among the various sleep stages was significantly more evident in patients with EDS. We concluded that patients with SRBD and EDS have a reduced BRS and an increased sympatho/vagal balance throughout the night, with an impaired modulation of LF/HF power ratio among the sleep stages (Lombardi et al., 2008). Although the cross-sectional nature of our study could not definitively establish a causal link between reduced BRS, altered cardiac autonomic modulation and EDS, alterations in baroreceptor afferent influences might result in an impaired bottom-up influence on the level of vigilance during wakefulness, while a top-down altered modulation of the same system could account for the onset of the cardiovascular complications of OSAS.

Whatever the mechanisms may be, our data suggest that exploring cardiac autonomic modulation during the night might help to identify SRBD patients at risk for reduced daytime vigilance. In turn, given the known prognostic value of changes in cardiac autonomic modulation, assessment of autonomic function in these patients may help to disclose one of the mechanisms potentially associated with an increased cardiovascular risk in this condition.

This hypothesis was recently supported by a cross-sectional multicenter study on 6046 subjects from the Sleep Heart Health Study demonstrating that the association of sleep-disordered breathing with hypertension is stronger in individuals who report daytime sleepiness than in those who do not. These findings emphasize the importance of taking the level of daytime somnolence into account to prevent cardiovascular events in patients with sleep-related breathing disorders (Kapur et al., 2008).

The cross-sectional nature of the available studies hampers a causal interpretation of the relation between changes in ANS function, cardiovascular complications and onset of daytime somnolence. However, it is unlikely that somnolence during the daytime is responsible for changes in ANS function during sleep. Both phenomena may depend on a common causative factor or on the bottom-up effects mentioned above. In addition, an altered ANS function may also affect the central neural mechanisms involved in the regulation of daytime vigilance.

This hypothesis may be indirectly supported by short-term studies failing to show any hypotensive effect of CPAP on 24 h ambulatory blood pressure in patients with severe OSAS but without EDS (Barbé et al., 2001; Robinson et al., 2006). However, a small decrease in blood pressure values in non-sleepy patients with OSAS may be observed over longer follow-up periods. Indeed, Barbé et al. showed a BP reduction in treated OSAS patients only after 1 year of CPAP treatment and only in patients who used the CPAP for more than 5–6 h per night (Barbé et al., 2010; Marrone et al., 2010).

In conclusion, all the evidence gathered so far supports the importance of autonomic function assessment, and more specifically baroreflex sensitivity measurement, both in pathophysiological and clinical settings. The availability of methods able to explore the features of “spontaneous” baroreflex cardiac modulation seems to be of great value in investigating the physiology of neural cardiac modulation during sleep and its derangement in pathologic conditions such as OSAS with or without EDS. Further studies are needed to clarify the prognostic relevance of these changes in relation to the risk of cardiovascular events reported in OSAS patients.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at doi:10.1016/j.autneu.2012.02.005.

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