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Review

Circadian rhythms of cardiovascular autonomic function: Physiology and clinical implications in neurodegenerative diseases

Francesca Baschieri[a], Pietro Cortelli[a,b,*,1]

[a] Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy
[b] IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica NeuroMet, Bologna, Italy

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ABSTRACT

Circadian rhythms of blood pressure and heart rate are regulated by a biological clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which modulates the autonomic nervous system activity directed to the heart and blood vessels. Humoral mediators released with periodicity induced by the SCN as well as sleep are also important factors. Disruption of physiological cardiovascular circadian rhythms has important clinical implications, as it is associated with increased morbidity and mortality. In this review, firstly we will give an overview on the neuroanatomic and physiologic aspects of cardiovascular circadian rhythms. Secondly we will examine how to assess them in clinical practice. Finally we will discuss certain neurodegenerative diseases in which there is an alteration of these rhythms, such as Parkinson's disease and Alzheimer's disease.

1. Introduction

Essential physiological functions are paced by a biological clock that sets a rhythm to alternate a period of activity to a period of repose. This rhythm mainly follows the light-dark cycle and is of approximately 24 hours, that is *circadian*. Sleep-wake cycle, behaviour, cognitive performance, feeding, metabolic processes, cardiovascular function and maintenance of body temperature are all regulated on a daily basis and present their own circadian profile. It takes a complex and intriguing combination of pathways to finely regulate and integrate each component within one another and eventually allow us to perform in the best and most appropriate way according to the time of day or night. Disruption of physiological circadian rhythms has detrimental effects and is associated with several pathological conditions including cardiovascular diseases (Portaluppi et al., 2012), obesity (Covassin et al., 2016) and neurodegenerative diseases (Musiek and Holtzman, 2016; Videnovic et al., 2014a). Moreover, medical conditions themselves display a 24-hour pattern in symptom presentation and intensity, for example cardiac arrhythmias and ischemic disease, respiratory illnesses such as asthma, allergic rhinorrhea and chronic obstructive pulmonary disease, and gastroesophageal reflux. This reflects the circadian trend of most physiological and environmental stimuli that are involved in pathogenesis of these conditions. The understanding of the 24-hour pattern of diseases is important for personalizing therapy and optimizing the time of drug administration (Smolensky et al., 2015).

This review will focus on circadian rhythms of cardiovascular autonomic function. Firstly we will describe how arterial blood pressure (BP) and heart rate (HR) are regulated throughout the 24-hour period. Secondly we will examine how to assess cardiovascular circadian rhythms by means of continuous monitoring of BP and HR, and other related tests that study the circadian system. Finally we will discuss certain neurological diseases in which there is an alteration of these rhythms.

2. Physiology

2.1. Cardiovascular autonomic system

Sympathetic and parasympathetic systems innervate the heart and blood vessels, thus regulating cardiac contractility, HR and vascular resistance, which are the main determinants for BP.

The heart has an intrinsic pacemaker activity that generates an

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SCN, suprachiasmatic nucleus; AVP, arginine-vasopressin; PVN, paraventricular nucleus; NREM, non-rapid eye movement; REM, rapid eye movement; MSA, multiple system atrophy; AF, autonomic failure; OH, orthostatic hypotension; PD, Parkinson's disease; DLB, dementia with Lewy bodies; PAF, pure autonomic failure; AD, Alzheimer's disease; HD, Huntington's disease; FFI, fatal familial insomnia

* Corresponding author at: IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica NeuroMet, Bologna, Italy.
E-mail address: pietro.cortelli@unibo.it (P. Cortelli).
[1] Postal address: IRCSS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica NeuroMet, Ospedale Bellaria, via Altura 3, 40139 Bologna, Italia.

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electric impulse, which is subsequently propagated to coordinate the contraction of the cardiac pump. Specialized cardiomyocytes with such properties are referred to as the cardiac conduction system, which comprises the sinoatrial node, the atrioventricular node, atrioventricular bundle, left and right bundle branches and Purkinje fibre network (van Weerd and Christoffels, 2016). HR is dictated by the activity of the sinoatrial node, whose cardiomyocytes have unstable resting membrane potential that undergoes spontaneous depolarization by the effect of several ion currents, thus generating the action potential that is responsible for each heartbeat. Contraction of the working cardiomyocytes of the ventricles is induced by the release of calcium from the sarcoplasmic reticulum (Liu et al., 2016).

The heart has a rich intrinsic and extrinsic autonomic innervation. The intrinsic cardiac nervous system is composed of ganglionated plexi and their axons embedded in the fat pads of the epicardium and the cardiac wall. The role of the intrinsic cardiac nervous system seems to be the modulation of the activity of the sinoatrial and atrioventricular nodes (Hou et al., 2007). The extrinsic autonomic innervation comprises the parasympathetic and sympathetic cardiac nerves. Vagal preganglionic cardiac neurons are located in the nucleus ambiguus and, to a lesser degree, in the dorsal vagal motor nucleus. Neurons located in the nucleus ambiguus are sensible to baro- and chemoreceptor inputs as well as central respiratory drive, to adjust the heart rate to changes in blood pressure and respiration. Vagal preganglionic fibres project to parasympathetic neurons in the cardiac ganglia that innervate the cardiac conduction system, atria and to some extent the ventricle muscle. The main neurotransmitter is acetylcholine, whose effects are the slowing of heart rate and atrioventricular conductance, and the decrease of contractility, largely via muscarinic M2 receptors (Gourine et al., 2016). The cardiac sympathetic preganglionic neurons are located in the intermediolateral cell column of the thoracic spinal cord, mainly at the T3 level. They synapse on the postganglionic neurons in the ganglia of the sympathetic chain, mainly in the stellate ganglion at the rostral thoracic level. Sympathetic postganglionic fibres innervate the cardiac conduction system and muscle. Sympathetic effects on the heart include increase in the sinoatrial node rate, decrease in the atrioventricular nodal conduction, and increase in myocardial contractility, thus increasing HR and cardiac output (Coote and Chauhan, 2016). The main neurotransmitter is noradrenaline, acting primarily via adrenergic β2 receptors.

Differences exist between left and right sympathetic and parasympathetic innervation to the heart, with great variability among individuals (Kawashima, 2005). It is noteworthy that left-sided cardiac sympathetic nerves are quantitatively dominant at the ventricular level (Schwartz et al., 2017). From a functional point of view, physiological studies showed that left sympathetic fibres predominantly influence cardiac inotropy, whereas right fibres mainly have chronotropic effects (Coote and Chauhan, 2016). Lateralization seems to be less marked when analysing stimulation effects of left versus right vagal nerve, suggesting a more homogenous distribution in parasympathetic effects to the heart (Yamakawa et al., 2014).

Arterial blood vessels in the peripheral tissues receive mainly sympathetic innervation, which exerts a constant action to maintain the arterial wall tone. Sympathetic activation induces vasoconstriction by releasing several neurotransmitters such as noradrenaline and adenosine triphosphate. In cranial and visceral vessels, parasympathetic fibres innervating blood vessels release acetylcholine and nitric oxide, eliciting primarily vasodilation (Sheng and Zhu, 2018).

The structure of the autonomic nervous system allows a beat-to-beat regulation of the cardiovascular parameters in response to endogenous (including respiration) and external, also unpredictable, stimuli. However, it also exerts a tonic, constant action that determines the day-night trend, under the influence of central nervous system circuits that will be discussed in the next paragraph.

2.2. Hypothalamus

The central biological clock is the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus (Hastings et al., 2018). There are also “peripheral” clocks, which also generate circadian rhythms in peripheral tissues and organs, modulated by the central one (Takahashi et al., 2008). The SCN has an intrinsic electric activity with a 24-hour period, but external stimuli, mostly the light-dark signal and others from the environment (e.g. temperature, food availability), as well as visceral sensory information and cortical inputs reinforce and entrain this pattern. The effectors that send information from the SCN to body targets are humoral mediators and the autonomic nervous system: together they synchronize “peripheral” clocks with the main one (Benarroch, 2008).

Circadian rhythms originate at a molecular level, where feedback loops regulate the transcription and translation of core “clock” genes (e.g. *CLOCK*, *BMAL*), as well as protein modification, interaction and degradation within the cell (Merbitz-Zahradnik and Wolf, 2015). Some of these genes are directly associated with the circadian BP profile, as demonstrated in several pre-clinical studies (Douma and Gumz, 2018).

The SCN transmits circadian information to the periphery, including heart and blood vessels, through multi-synaptic pathways. The main neurotransmitter of SCN neurons is GABA. The SCN is subdivided into a core and shell subregions, which contain subpopulations of GABAergic neurons that differ in their connectivity and expression of neuropeptides. The core contains neurons that synthesize vasoactive intestinal polypeptide and receives glutamatergic inputs from melanopsin ganglion cells of the retina via the retinohypothalamic tract; these inputs entrain the circadian clock with the light-dark cycle. The shell contains neurons that express arginine-vasopressin (AVP), receive paracrine inputs from vasoactive intestinal polypeptide neurons, and participate in coupling between SCN neurons; the core and the shell interact via reciprocal GABAergic connections. Astrocytes participate in the synchronization with the SCN via local release of glutamate. Neurons of the SCN regulate autonomic function via GABAergic inputs, either directly or via the subparaventricular zone, to the paraventricular nucleus (PVN) and dorsomedial nucleus of the hypothalamus (Benarroch, 2008). These nuclei contain “pre-autonomic” neurons that project to sympathetic and parasympathetic neurons in brainstem and spinal cord nuclei (Saper et al., 2016). Neurons of the PVN initiate autonomic responses to internal stressors, such as hypoglycemia, hypovolemia, or cytokines; those in the dorsomedial nucleus initiate sympathoexcitatory responses to external stressors and exposure to cold temperature (Silvani et al., 2016). The perifornical region of the dorsomedial nucleus, as well as the adjacent lateral hypothalamus, contains a population of hypocretin/orexin neurons (Grimaldi et al., 2014) that are active during arousal and sends projections not only to arousal regions of the brainstem such as the locus coeruleus but also to brainstem autonomic areas. There are reciprocal direct and indirect interactions between hypocretin/orexin and SCN neurons.

Studies on animal models demonstrated that a high level of specialization exists in the PVN, with pre-autonomic neurons that selectively project to the sympathetic or parasympathetic branches (Buijs et al., 2003). PVN neurons that project to autonomic nuclei synthesize AVP, oxytocin, corticotrophin releasing hormone, encephalin, dynorphin, angiotensin II and glutamate (Benarroch, 2005). Neurons of the dorsomedial nucleus utilize glutamate. Both the PVN and the dorsomedial nucleus receive dense innervation from the hypocretin/orexin neurons in the perifornical region.

Regarding hormones, melatonin and cortisol represent major players in the circadian system. They exert effects on almost every tissue and organ of the body, regulating other cyclic biological, including cardiovascular, functions. Melatonin is produced in the pineal gland, and both its synthesis and secretion display a strong circadian rhythm, with increasingly higher levels during darkness (night-time in humans), and very low values during daytime. Melatonin derives from

serotonin, which undergoes first acetylation and then methylation in the pineal gland cells. Melatonin synthesis is activated by norepinephrine released from terminals of the superior cervical ganglion and is regulated by the SCN in response to the light-dark stimuli. From photosensitive ganglion cells of the retina, the light stimulus reaches the SCN via the retinohypothalamic tract. The SCN has an inhibitory influence on sympathoexcitatory neurons of the PVN projecting to the intermediolateral cell column. Activation of the SCN neurons by light results in inhibition of this sympathoexcitatory pathway to the superior cervical ganglion and thus reduced melatonin secretion (Benarroch, 2008).

Cortisol is also secreted with a robust circadian rhythmicity. Serum values are low during the night and increase gradually during early morning hours to a peak at awakening. Throughout the 24 h, hourly variations in cortisol levels are observed, that are "ultradian" rhythms, which reflect its pulsatile secretion. Cortisol production is mainly under the influence of the hypothalamic-pituitary-adrenal axis: the PVN of the hypothalamus releases in the portal circulation corticotropin-releasing hormone and AVP, which stimulate the release of adrenocorticotropic hormone by the anterior pituitary gland in the systemic circulation. Adrenocorticotropic hormone reaches the adrenal gland cortex and stimulates cortisol production. Cortisol circadian rhythm is entrained by the SCN, which firstly modulates corticotropin-releasing hormone release via connections with the PVN thus regulating hypothalamic-pituitary-adrenal axis activity, and secondly sends projections to the adrenal gland via the sympathetic nervous system to modulate adrenal sensitivity to adrenocorticotropic hormone. These mechanisms entangle with the "peripheral" adrenal clock (Son et al., 2018; Spiga et al., 2014).

Fig. 1 summarizes the cardiovascular circadian system.

2.3. *Heart rate and blood pressure circadian rhythms: relationship with the sleep-wake cycle*

In a healthy subject who is awake during the day and sleeps at night, the physiological circadian profiles of BP and HR are well known. HR decreases during the night with mean values of approximately 6 bpm less than those occurring during the day, and increases in the early morning (Palma and Benarroch, 2014; Scheer et al., 2003). The main determinant of the HR circadian rhythm is the circadian parasympathetic tone to the heart, whereas the morning surge depends on the sympathetic drive upon light exposure (Scheer et al., 2004).

BP typically falls during night-time of about 10–20% compared to daytime values (the so called "dipping" pattern). It gradually increases in the early morning to a peak at awakening time. Other two peaks occur after 2–3 h after awakening and in the early evening (Smolensky et al., 2017). Autonomic nervous system activity is a main determinant for BP: much information in this regard has been obtained from studies involving microneurography, which records nerve activity from intraneural microelectrodes inserted percutaneously into a peripheral nerve. Muscle and skin sympathetic nerve activity recordings under different conditions are useful to assess sympathetic efferent activity (Vallbo et al., 2004). Muscle sympathetic nerve activity induces vasoconstriction and thus influences BP by regulating peripheral resistance. Diurnal BP profile and variability is related to sympathetic activity which predominates during wakefulness and decreases during sleep (Narkiewicz et al., 2002; Somers et al., 1993). However, there are several other elements that contribute to BP rhythmicity. BP is the result of the interrelation of cardiac output and peripheral vascular resistance. Therefore, other hormonal systems that influence anyone of these parameters eventually modify BP. These include the renin-angiotensin-aldosterone system, hypothalamic-pituitary-adrenal axis, renal function and mediators released at the endothelial level (Smolensky et al., 2017).

The trend of BP and HR variations described above cannot be separated from a thorough discussion on the sleep-wake cycle. Indeed, BP and HR are strictly dependent on the specific sleep stage and sleep is closely associated with autonomic nervous system function (Calandra-Buonaura et al., 2016). During non-rapid eye movement (NREM) sleep stages (from stage 1 to 3) BP and HR decrease gradually and set at lower mean values. This is due to a gradual decrease in sympathetic activity and prevalence of parasympathetic tone. K-complexes (a well-delineated, high-amplitude, negative, sharp wave immediately followed by a positive component) and arousals may be accompanied by transient bursts in sympathetic activity and therefore transient surges in BP and HR. During rapid eye movement (REM) sleep (20–25% of total sleep time) parasympathetic tone still prevails, but intermittent bursts of sympathetic activity cause marked fluctuations in BP and HR (Somers et al., 1993). Because REM sleep is more represented during early morning hours, such hemodynamic changes have a causal link with the highest rates of cardiovascular and cerebrovascular events during such period, including ischemic and hemorrhagic stroke, myocardial infarction and sudden cardiac death (Hanak and Somers, 2011). Clock time of certain events such as acute myocardial infarction and ventricular fibrillation may also affect disease severity and survival, with early morning occurrences being associated with worse prognosis (Manfredini et al., 2013). BP follows similar variations also during daytime sleep, suggesting a stronger association, compared to HR, with the sleep-wake cycle (Cortelli et al., 1996). Indeed, studies of the circadian control of cardiovascular function in healthy humans performed under constant environmental conditions (Duffy and Dijk, 2002) provided evidence supporting an endogenous circadian rhythm independent of the effects of rest-activity for HR but not for BP (Van Dongen et al., 2001).

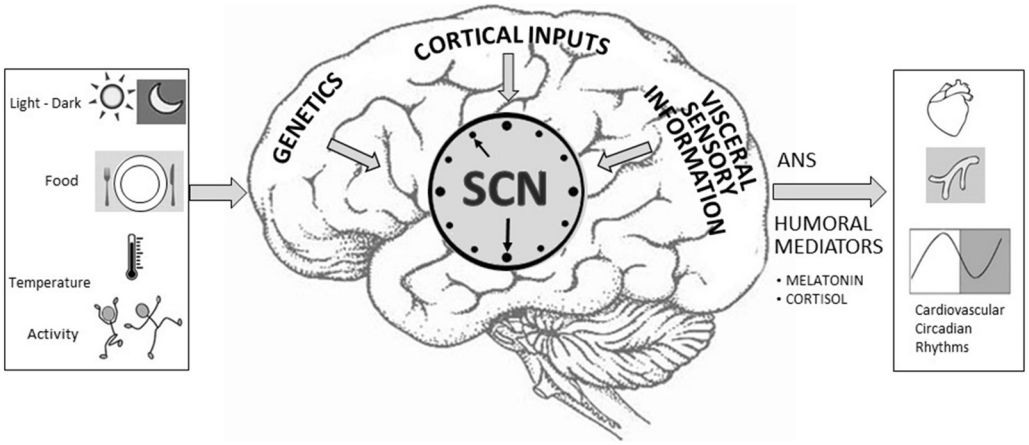

Fig. 1. Basic scheme of the cardiovascular circadian system. The SCN is the master clock that sets the rhythm. Environmental clues such as the light-dark stimulus, meal schedule, temperature and physical activity, as well as endogenous signals, entrain such rhythm. The SCN effectors are the autonomic nervous system and humoral mediators (e.g. melatonin, corticotropin-releasing hormone – adrenocorticotropic hormone – cortisol axis). They act by direct effect on autonomic neurons directed to heart and blood vessels and systemic modulation of other parameters that eventually influence blood pressure.

2.4. Assessment of cardiovascular circadian rhythms

Cardiovascular circadian rhythms are assessed by means of continuous monitoring of systolic BP (SBP), diastolic BP (DBP) and HR for at least 24 h. At our Institution, this is performed with a non-invasive, beat-to-beat continuous monitoring of BP and HR in a standardized procedure (Grimaldi et al., 2013). During the exam, patients remain in a temperature- and humidity-controlled room, with a dark period from 23:00 to 07:00, and are allowed to sleep at their own will except during eating time. Food intake is divided into three meals and three snacks at defined hours and calories. Alcohol, coffee and tea are avoided from the night preceding the exam. Drugs are also withheld, when possible. Considering the close association between cardiovascular parameters and sleep, in order to better evaluate the circadian variation of BP and HR in relation to the sleep-wake state, a polygraphic recording including EEG, right and left electro-oculograms, ECG, and electromyogram of the mylohyoideus and anterior tibialis muscles is also performed at the same time. For analysis, difference between mean daytime and night-time SBP, DBP and HR values are calculated. Three nocturnal BP patterns can be recognized: (1) “dipping”, if mean BP at night falls ≥10% compared to daytime values; (2) “reduced-dipping”, if the nocturnal BP fall is < 10%; (3) “non-dipping or rising”, if BP does not decrease or increases compared to daytime. HR variations follow similar patterns. The physiological profile is the dipping pattern; reduced-dipping and non-dipping patterns are pathological and require treatment and follow-up (Fanciulli et al., 2018). The following step of the analysis is the evaluation, by means of statistical procedures, of parameters such as phase, amplitude and period, which define the presence of rhythmicity in the SBP, DBP and HR time series, whether such rhythmicity is within a 24-hour period, and its characteristics.

Using standardized procedures is important to reduce the effects of those variables that influence cardiovascular function and thus “mask” the inherent circadian rhythm. These include for example food intake, light intensity, environmental temperature, physical activity, and of course the sleep-wake cycle. In clinical practice it is not possible to eliminate such factors completely. Moreover, around-the-clock BP monitoring is often performed in ambulatory care, with an automated upper arm cuff and readings every 30 min during the day and every 60 min during the night (Whelton et al., 2017). While it is more difficult in this case to ascertain the effects of confounding variables, it is still a useful exam which allows the detection of BP trend during the patient's everyday life and, therefore, “actual” BP values. It is important to instruct the patient to keep a diary to precisely record activities, time of the meals, sleep times, and so on.

Additional information on the pathophysiology of cardiovascular circadian function can be gathered indirectly from the study of other biological circadian rhythms, which also depend on the integrity of the hypothalamic and other autonomic central structures that regulate periodicity. For example, the study of the circadian rhythm of body core temperature could be useful. It is performed by continuous monitoring of rectal temperature every 2 min with a portable device, with the same standardized method required for BP and HR (Pierangeli et al., 2001). Serial and frequent measurements over the 24 h of serum levels of melatonin and cortisol, the two main hormones under the control of the SCN, provide good indexes of the integrity of the circadian system (Claustrat and Leston, 2015; Selmaoui and Touitou, 2003). Moreover, both of these hormones affect cardiovascular physiology and their abnormal secretion may directly contribute to the pathological BP night pattern (Fabbian et al., 2013).

3. Clinical implications in neurodegenerative diseases

Abnormalities in circadian rhythms, including those of cardiovascular function, are frequently encountered in neurodegenerative diseases, as it will be discussed in the following section. In such conditions, cardiovascular autonomic dysfunction is quite common and it is important for pathophysiological considerations. The cardinal feature of cardiovascular autonomic failure (AF) is neurogenic orthostatic hypotension (OH), defined as a sustained reduction of SBP of at least 20 mm Hg and/or DBP of at least 10 mm Hg within 3 min of standing or head-up tilt test (Freeman et al., 2011), and associated supine hypertension defined as SBP of ≥140 mm Hg and/or DBP of ≥90 mm Hg measured after at least 5 min of rest in the supine position (Fanciulli et al., 2018). Symptoms of OH comprise light-headedness, dizziness and visual disturbances that typically occur on standing and recover completely by laying flat. It may also cause syncope (Mathias, 2003). There is diurnal variability in severity of OH degree and symptoms, which is usually worse in the morning upon awakening and gradually ameliorate over the day. Conversely, supine BP in patients with AF is lowest in the morning and increase during the day to prevail in the evening and at night-time (Mathias et al., 2013). The main mechanisms involved are likely to be nocturnal polyuria and natriuresis typical of patients with AF, which cause fluid depletion (Mathias et al., 1986), and a decrease in cardiopulmonary blood volume due to overnight fluid redistribution, with subsequent reduced cardiac output in the morning compared to the evening (Omboni et al., 2001). It is interesting noting that orthostatic intolerance that may lead to syncope in healthy adults without AF (i.e. vasovagal syncope) is also more prominent in the early morning (Lewis et al., 2010). A study performed on healthy subjects found evidence that the circadian system might directly modulate vasovagal responses to orthostatic stress, thus leading to increased susceptibility to syncope at specific times of the day (Hu et al., 2011).

3.1. α-Synucleinopathies

α-Synucleinopathies are a group of neurodegenerative diseases of the central nervous system characterized by deposits of the protein α-synuclein in different structures. In such conditions, the evaluation of cardiovascular autonomic function is important not only to guide the diagnosis but also for therapeutic and prognostic reasons (Fanciulli et al., 2013). Cardiovascular circadian rhythms also proved to be impaired in most cases. It is worth noting that α-synucleinopathies are often associated with sleep disorders, including insomnia, excessive daytime sleepiness, REM sleep behaviour disorder, restless leg syndrome and sleep related breathing disorders (Chahine et al., 2017). Therefore, considering the close association between sleep and cardiovascular function, sleep studies are useful when assessing cardiovascular circadian rhythms in such patients.

3.1.1. Multiple system atrophy

Multiple system atrophy (MSA) is characterized by AF (mainly cardiovascular and/or urinary) associated with any combination of poorly levodopa-responsive parkinsonism, cerebellar and pyramidal signs (Quinn, 1989). The disease carries a poor prognosis with mean life expectancy of about 9 years from onset (Low et al., 2015; Wenning et al., 2013). Early onset cardiovascular dysautonomia is an unfavourable predictor of survival, and thorough autonomic testing is highly recommended not only as a diagnostic tool but also as a prognostic marker (Calandra-Buonaura et al., 2013; Coon et al., 2015). OH and associated supine hypertension in MSA are prominent and severe. Diagnostic criteria for the diagnosis of probable MSA requires a decrease of BP within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic (Gilman et al., 2008), as these are more appropriate values in the setting of supine hypertension. The study of BP and HR circadian rhythms in MSA by means of 24-hour ambulatory BP monitoring showed an absence of the physiological nocturnal BP fall (either non-dipper or reverse pattern) and blunted HR decrement, with prevalence up to 96% of the patients (Fanciulli et al., 2014; Plaschke et al., 1998; Reimann et al., 2010; Schmidt et al., 2009; Vichayanrat et al., 2017).

Neuronal loss and glial cytoplasmic inclusions, the pathological hallmarks of MSA containing α-synuclein, affect several structures of

the central nervous system including substantia nigra, putamen, caudate, vermis, cerebellar hemisphere, inferior olivary nucleus, locus coeruleus, autonomic system nuclei of the hypothalamus and brainstem, and intermediolateral cell column and Onuf's nucleus, to varying degree according to the predominant phenotype (Ahmed et al., 2012). Autonomic failure in MSA is therefore caused by neurodegeneration of the preganglionic sympathetic neurons and supraspinal nuclei responsible for the integrated control of cardiovascular autonomic function, especially the rostral ventrolateral medulla (Benarroch, 2002; Coon et al., 2018). The pathophysiology underlying cardiovascular circadian rhythm disruption is still to be clarified. A recent histopathological study assessing the presence of α-synuclein inclusions in the key structures of the circadian system failed to show inclusions both in the SCN and in the pineal gland of MSA cases, suggesting that circadian dysfunction might be secondary degeneration of autonomic networks (De Pablo-Fernandez et al., 2018). Loss of AVP neurons in the SCN and in the posterior subnucleus of the PVN might be implicated in the impaired autonomic control of circadian BP rhythm (Benarroch et al., 2006). Glial cytoplasmic inclusions were detected in the perifornical area containing hypocretin neurons, which were decreased in number compared to controls (Benarroch et al., 2007).

3.1.2. Parkinson's disease

Parkinson's disease (PD) is the most common cause of parkinsonism. Classically considered to be a pure movement disorder entity, it is now well recognized that it is very heterogeneous comprising a wide spectrum of non-motor features such as sleep disorders, cognitive impairment and indeed AF (Langston, 2006). Prevalence of OH in PD is estimated at around 30%, with large variety between studies (Velseboer et al., 2011). Twenty-four-hour ambulatory BP monitoring showed abnormal nocturnal BP profile in up to 48% of PD patients (Fanciulli et al., 2014; Reimann et al., 2010; Schmidt et al., 2009), usually associated with dysautonomia detected with cardiovascular autonomic tests (Milazzo et al., 2018). However, pathological trends were described also in patients without OH, even though to a lesser degree (Vichayanrat et al., 2017). One study did not find abnormalities in the circadian profile of BP and HR in PD without cardiovascular AF (Plaschke et al., 1998). Reduction of the physiological nocturnal HR decline in PD seems to be less pronounced than in MSA (Pilleri et al., 2014).

The neuropathological substrate for cardiovascular AF in PD is related to degeneration and Lewy bodies (i.e. neuronal cytoplasmic inclusions of α-synuclein) involving mainly post-ganglionic sympathetic fibres (Goldstein, 2003). Affected brain premotor cardiovascular autonomic nuclei include the insular cortex, hypothalamus, rostral ventrolateral medulla, and dorsal motor nucleus of the vagus, although to a lesser degree compared to MSA (Cersosimo and Benarroch, 2012; Coon et al., 2018; Iodice et al., 2011). Alpha-synuclein deposition was demonstrated in the SCN of PD cases, providing evidence for a direct involvement of the circadian structures in this condition, also at mild disease stages (De Pablo-Fernandez et al., 2018). Indeed, 24-h monitoring of serum melatonin levels in PD patients under modified constant routine conditions showed a blunted circadian rhythm compared to controls (Videnovic et al., 2014b). Patients with PD presented a significant reduction of the number of hypocretin neurons and hypocretin concentration in the ventricular cerebrospinal fluid compared to controls (Fronczek et al., 2007).

PD is a sporadic disease in most cases. However, genetic research has discovered that about 5–10% of cases are monogenic forms with an autosomal dominant or recessive inheritance, thus unravelling some pathogenic aspects of α-synucleinopathies (Sheerin et al., 2014). One of the involved genes is *SNCA*, encoding α-synuclein itself. Point mutations and whole-locus multiplications of this gene were identified as a rare cause of familial autosomal dominant PD (Elia et al., 2013; Pasanen et al., 2014). Genetic PD associated with duplications and triplication of the *SNCA* gene might be considered the most pure form of α-synucleinopathies, as they get excess of α-synuclein. Interestingly, cardiovascular AF is described in almost all cases, with earlier onset and more severe phenotype in patients with triplication rather than duplication, suggesting a dose-related phenomenon (Chelban et al., 2018). To further support this hypothesis, some genetic forms of PD do not show Lewy bodies (for example those associated with mutations in *PARK2* gene and some in *LRRK2* gene) and they usually have no AF, pointing to a close relationship between α-synuclein and autonomic involvement (Chelban et al., 2018). However, this link might not be as easy as it looks. A rare genetic form of α-synucleinopathy is caused by mutation in *PLA2G6* gene and presents with adult-onset dystonia-parkinsonism. It is usually classified within the group of neurodegeneration with brain iron accumulation syndromes, although iron deposition is not always present, and pathology shows Lewy bodies and tau (Paisán-Ruiz et al., 2012). Intriguingly, AF is hardly reported in these patients (Karkheiran et al., 2015). In the described cases of genetic PD, autonomic evaluation is based on clinical history, presence of OH, and study of the cardiac adrenergic innervation. Further studies on autonomic function including BP and HR circadian rhythms in genetic forms of PD are warranted, and promise exciting results.

3.1.3. Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is characterized by prominent cognitive decline associated with visual hallucinations and fluctuation in attention and alertness, appearing before or within one year from the onset of parkinsonian features (McKeith et al., 2017). Cardiovascular AF is frequent and severe in DLB, supports the diagnosis (Thaisetthawatkul et al., 2004) and negatively impacts on survival (Stubendorff et al., 2012). In a study assessing the 24-h profile of cardiovascular function in DLB, non-dippers were about 82% of the patients (Kim et al., 2015). The neuropathological basis for cardiovascular AF in DLB is similar to that in PD (Coon et al., 2018). Studies evaluating the pathophysiology for circadian disruption are lacking. Prominent atrophy of the hypothalamus is noticed on brain MRI (Whitwell et al., 2007). No significant α-synuclein pathology was found in the PVN (Diodati et al., 2012). Significant loss of hypocretin neurons in the lateral hypothalamus was observed (Kasanuki et al., 2014).

At very early disease stages, some clinical features of different types of dementia with different underlying pathology (including DLB and Alzheimer's disease (AD) that will be discussed later) might overlap. A precocious diagnosis is warranted for prognostic and therapeutic reasons, especially as new disease-modifying therapies are being developed and tested on patients with short disease duration. Biomarkers in the cerebrospinal fluid and brain imaging findings are very helpful in guiding the diagnosis. It would be interesting to accurately study and compare circadian rhythms at very early stages between distinct types of dementia: the different pathophysiology behind such conditions might differently affect structures involved in the control of circadian periodicity, thus adding information that could help in the differential diagnosis as well as suggesting a better therapeutic approach.

3.1.4. Pure autonomic failure

Pure autonomic failure (PAF) is a rare disease characterized by progressive, mainly cardiovascular AF, without any other neurological sign (The Consensus Committee of the American Autonomic Society and the American Academy of Neurology, 1996) and with at least a 5-year history of duration (Freeman, 2004) (to distinguish it from other diseases presenting with autonomic symptoms but soon evolving into parkinsonian syndromes). Response to treatment is generally good and the prognosis benign. The main clinical feature is OH. About 50% to 100% of patients present also supine hypertension (Biaggioni and Robertson, 2002; Goldstein et al., 2003a, 2003b). Twenty-four-hour ambulatory BP monitoring showed a non-dipping pattern during sleep in up to 90% of the patients (Struhal et al., 2013). Consequences include cardiac organ damage and arterial stiffness (Milazzo et al., 2015).

Pathology in PAF is mainly restricted to degeneration of the

peripheral (postganglionic) autonomic nervous system, where Lewy bodies can be found (Thaisetthawatkul, 2016). Mild Lewy body pathology has been described also in the central nervous system, particularly in the substantia nigra and locus coeruleus, in few autoptic studies of patients with long-standing isolated AF (Hague et al., 1997). It could be argued that, had these patients lived longer, they would have developed PD. Nonetheless, at that stage, the involvement of the central nervous system is minor compared to that of the peripheral autonomic nervous system, and does not seem to explain the abnormality of circadian rhythms. OH can be attributed to deficient noradrenaline synthesis and release from peripheral sympathetic nerve terminals, thus reduced increments upon standing in plasma noradrenaline levels (Goldstein et al., 2003a, 2003b). Supine hypertension seems to be related to preserved renin – angiotensin system pathway and increased mineralocorticoid receptors activation (Arnold et al., 2016). More studies are needed to evaluate the mechanism underlying abnormalities of circadian rhythms in PAF. An accurate study of the circadian system in patients with isolated AF that are prospectively followed up might be helpful to identify red flags for conversion to other α-synucleinopathies.

3.2. Alzheimer's disease

AD is the most common cause of neurodegenerative dementia around the world. AD manifests with gradual, progressive cognitive decline affecting mainly anterograde memory, executive functions and language. Atypical presentations are also described. Abnormally folded β-amyloid and tau proteins that deposit in plaques and neuronal tangles respectively are the main causative agents of the disease (Scheltens et al., 2016).

OH is common in patients with AD, although cardiovascular reflex tests assessing the integrity of both sympathetic and parasympathetic functions show responses that range from normal or only mildly impaired to severe impairment involving mainly the sympathetic branch (Allan et al., 2007; Jensen-Dahm et al., 2015).

Circadian rhythm dysfunction is well known in AD patients. A non-dipping or reverse dipping pattern of BP was observed in about 76% of the patients, mainly affecting SBP (Chen et al., 2013). Despite the good tolerability of ambulatory BP monitoring in patients with dementia (Conroy et al., 2016), not many studies have addressed cardiovascular circadian rhythms in AD. Other circadian rhythms are also affected. Patients with AD present rest-activity rhythm fragmentation and decreased amplitude (Musiek et al., 2018), significant phase-delay of body core temperature rhythm (Harper et al., 2001), and a blunted circadian rhythm of melatonin with decreased serum levels during night-time (Wu et al., 2003). Sleep is fragmented, with long nocturnal awakenings and excessive daytime sleepiness with diurnal naps; sleep architecture is also deregulated, with scarce representation of REM and NREM deep stages (Van Erum et al., 2018).

The SCN is affected by AD pathology (Baloyannis et al., 2015; Swaab et al., 1985), with significant decrease in the number of vasoactive intestinal polypeptide-expressing neurons (Zhou et al., 1995). The PVN is relatively spared instead (Goudsmit et al., 1990). The hypocretin system is also affected, with a loss of about 40% of hypocretin neurons and lower cerebrospinal fluid hypocretin levels in advanced AD compared to controls (Fronczek et al., 2012).

Elevated BP is recognized as a strong risk factor for cerebrovascular disease and dementia; a relationship between hypertension and ß-amyloid pathology has also been demonstrated (Hughes et al., 2018). Therefore, a non-dipping pattern of BP rhythm might actively contribute to disease progression. The study of cardiovascular circadian rhythms in patients with AD is important to recognize this condition and start appropriate treatment for BP. Prospective studies to evaluate the specific role of elevated BP and its treatment on the progression and outcome of patients with AD are needed.

3.3. Huntington's disease

Huntington's disease (HD) is a neurodegenerative disorder characterized by psychiatric disturbances, dementia and movement disorders, usually of the hyperkinetic type such as chorea, tics, dystonia and athetosis. It is a genetic condition transmitted in an autosomal dominant fashion, due to CAG triplet repeat expansion in the *HTT* gene on chromosome 4, encoding for the huntingtin protein. The mutant protein is toxic and induces neurodegeneration that primarily involves the basal ganglia (caudate and putamen). The number of repeats determines whether the disease will manifest: with more than 39 repeats HD will occur, whereas between 36 and 39 repeats HD may or may not occur. HD usually manifests in adulthood, between 30 and 40 years of age, and it is subjected to anticipation, that is an earlier onset in subsequent generations due to triplet expansion especially from the paternal line (McColgan and Tabrizi, 2018).

Cardiovascular autonomic dysfunction is described in HD, even in pre-symptomatic and early symptomatic stages, although it is not severe nor a predominant feature (Andrich et al., 2002; Bär et al., 2008; Kobal et al., 2010).

Abnormalities in circadian rhythms are actually prominent in this condition, although studies assessing them, especially cardiovascular ones, are relatively lacking. This might be explained by technical difficulties in recording patients affected by chorea and cognitive disturbances, with possibly associated treatments. A non-dipping BP pattern during the night was found in approximately 48% and 87% of pre-symptomatic mutation carriers and patients with HD respectively (Bellosta Diago et al., 2018). Disruption of circadian periodicity was also shown in studies on rest-activity and sleep-wake cycles. Patients with HD stayed longer in bed and presented increased nocturnal motor activity compared with controls (Morton et al., 2005). Regarding sleep structure, shorter total sleep time, reduced sleep efficiency and increased number of awakenings and arousals have been described in HD patients (Piano et al., 2015), who often report excessive daytime somnolence (Videnovic et al., 2009). Serum levels of cortisol and melatonin over the 24 h are also abnormal. In HD, analysis of serum cortisol levels rhythmicity showed a significant higher amplitude (Aziz et al., 2009b), whereas melatonin showed a delayed onset (but not offset) time (Aziz et al., 2009a).

Indeed, neuropathological studies have shown involvement of the SCN in HD, which may contribute to circadian dysfunction. The SCN shows a significant reduction of AVP and vasoactive intestinal polypeptide neurons (van Wamelen et al., 2013), along with cytoplasmic inclusions of mutant huntingtin (Aziz et al., 2008). Loss of orexin neurons in the lateral hypothalamus (Petersén et al., 2005) and vasopressin neurons in the PVN (Gabery et al., 2015) may also play a role. Van Wamelen and colleagues did not find significant neuronal loss in the PVN, but rather an imbalance between neurons expressing AVP and oxytocin, suggesting that the imbalance between these two may play part in the development of autonomic dysfunction (van Wamelen et al., 2012). Dysfunction in the dopaminergic postsynaptic system involving the hypothalamic-pituitary axis has been shown in a PET study (Politis et al., 2008). Precise mechanisms linking the mutant protein, hypothalamic pathology and cardiovascular circadian rhythms are still to be clarified.

3.4. Fatal familial insomnia

Fatal familial insomnia (FFI) is a rare prion disease caused by mutation in the codon 178 of the prion protein gene (*PRNP*), transmitted with an autosomal dominant pattern (Medori et al., 1992). The main target of pathology is the thalamus, in particular the medio-dorsal and anterior-ventral nuclei (Lugaresi et al., 1986). The study of FFI, whose cardinal signs are profound disruption of the sleep-wake cycle and vegetative dysfunction, has shed light on the role of thalamus in the regulation of these cyclic biological functions. As the name itself

implies, the disease is invariably fatal, with mean life expectancy of approximately 18 months from onset. Presenting features are insomnia with disturbances of vigilance during the day, accompanied by autonomic signs such as hypertension, tachycardia, hyperthermia, and hyperhidrosis. As the disease progresses, the patient falls into a state of oneiric stupor and acting dreams. This is associated with development of other neurological signs including unsteady gait, cerebellar ataxia, myoclonus, dysarthria, dysphagia, and pyramidal signs. Eventually the patient is bedridden in a sort of vegetative state. Death occurs suddenly or as a consequence of infection, usually respiratory (Montagna et al., 2003).

In brief, sleep is characterized by complete disruption of the cyclic organization and transition from one stage to another. Spindles and K complexes are not recognizable. Eventually, NREM stage 1 predominates during both day and night, with short clustered REM sleep episodes during which the patients usually display motor activity, mimicking daily-life gestures (Lugaresi et al., 2011).

Autonomic function was evaluated by means of cardiovascular reflex tests and pharmacological probes, overall showing results consistent with sympathetic hyperactivity and preserved cardiac parasympathetic function (Cortelli et al., 1991). Continuous 24-hour monitoring showed persistently increased values of BP and HR (Lugaresi et al., 1986) [Fig. 2]. The 24-hour rhythmicity was preserved although with reduced circadian variation until late stages, when it became completely abolished. Remarkably, in FFI there is a loss of the close synchronism that is usually present in the BP and HR cyclic patterns. While BP was affected more deeply at early stages, with more pronounced reduction in amplitudes of the 24-h components and phase shift so that physiological nocturnal dipping was lost, nocturnal bradycardia could still be detected to some extent until advanced stages, although with reduced amplitudes (Portaluppi et al., 1994a). This adds evidence firstly to the fact that circadian variation in HR is modulated differently than that of BP, and secondly that sleep plays only a partial role in the nocturnal decline of HR. Hormonal circadian variations, including those of catecholamines, cortisol, and melatonin, showed abnormal amplitudes and progressively declined until complete rhythm obliteration in terminal phases (Avoni et al., 1991; Portaluppi et al., 1994b) [Fig. 2]. Both serum cortisol and catecholamines were constantly higher compared to controls, and could contribute to hypertension (Portaluppi et al., 1994a). In summary, FFI is characterized by severe dysautonomia with exaggerated sympathetic activation; the 24-hour rhythmicity of cardiovascular and endocrine function is preserved until late disease stages, although parameters such as amplitudes and phase could be disrupted from earlier. The morphological, relatively selective involvement of the thalamus compared to other structures implicated in autonomic control (such as hypothalamus and brainstem) does not completely explain the pathophysiological mechanism behind such manifestations, which seems an exaggerated central sympathetic drive from supramedullary structures. More studies are needed to elucidate the role of the thalamus in maintaining autonomic and endocrine homeostasis and rhythms (Benarroch and Stotz-Potter, 1998).

4. Conclusions and perspectives

Circadian rhythm abnormalities are associated with increased morbidity and mortality in patients affected by neurodegenerative diseases. In clinical practice, when an impairment of the physiological circadian variation of cardiovascular function is suspected, 24-hour continuous monitoring of BP and HR is performed. For research purposes, a polygraphic recording to evaluate, in addition, sleep characteristics is warranted and preferable whenever possible, considering the close association between sleep and cardiovascular autonomic system. Adding the monitoring of body core temperature, melatonin and cortisol levels may provide additional information on the integrity of the circadian “clock” and might be useful when interpreting the

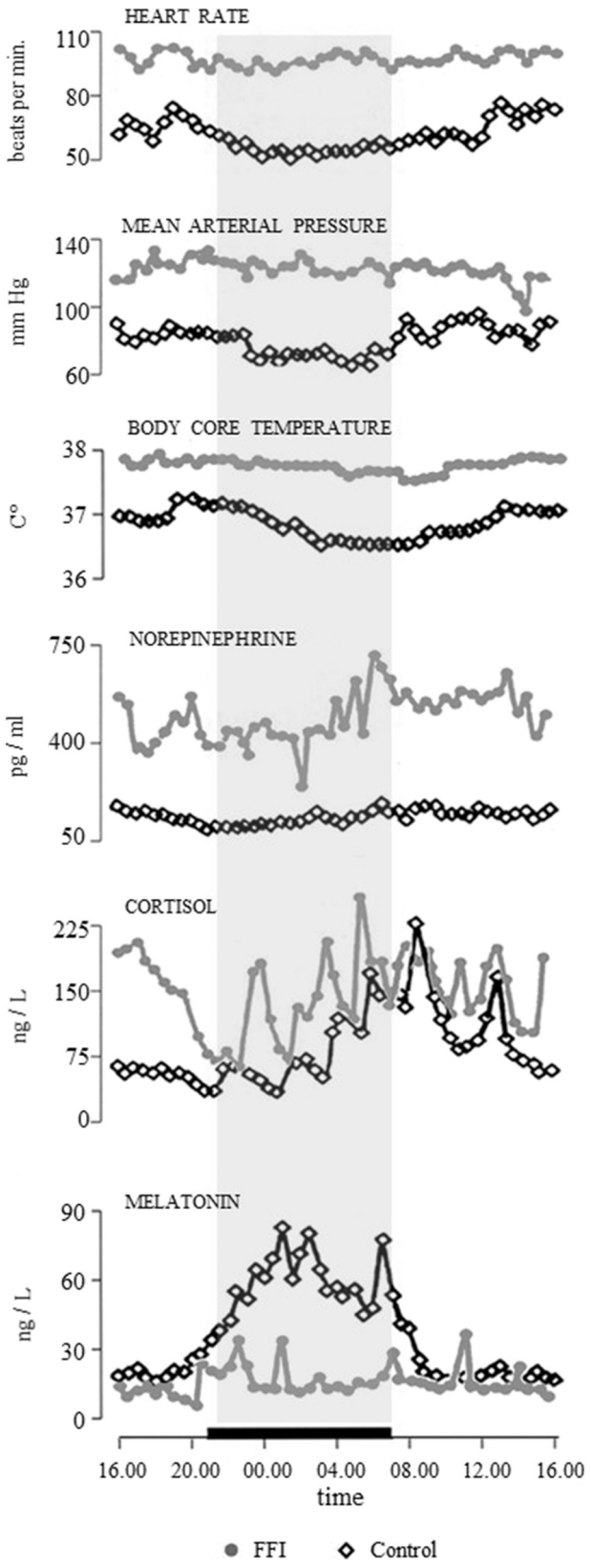

Fig. 2. Circadian rhythms in FFI. Twenty-four hour recordings of heart rate, blood pressure, core body temperature and plasma levels of norepinephrine, cortisol and melatonin in a patient with FFI compared to a healthy control. The grey shadowing indicates light-out period (night).

results. The link between circadian abnormalities and neurodegeneration is complex and more studies elucidating the precise pathophysiological mechanism underlying such abnormalities are needed. A better understanding of the anatomical and physiological basis of circadian rhythm alterations will allow the development of therapeutic approaches. Assessment of circadian rhythms is important to personalize treatment, including timing of drug administration to find the proper "circadian time". Considering the large impact that neurodegenerative diseases have worldwide, more efforts addressing such conditions also from the point of view of chronobiology are important and promise interesting results.

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