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Review

Insomnia and cardiovascular autonomic control

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A B S T R A C T

Insomnia is the most prevalent sleep disorder, particularly among middle and older aged adults, and is associated with a variety of negative health consequences, including higher risk for cardiovascular disease. Unfortunately, the mechanisms linking insomnia with cardiovascular risk remain largely unknown, thus limiting targeted therapeutic interventions. The hyperarousal hypothesis has attracted the most support, positing that insomnia is a result of multisystem over-activation, including sympathetic hyperactivity, which promotes wakefulness and blocks the occurrence of sleep at the desired time. The results from literature in support of this hypothesis are inconclusive and mainly relay on studies that used methods to assess sympathetic activity lacking in specificity and reproducibility. The present review aims at summarizing the primary findings on autonomic nervous system regulation in insomnia while highlighting the advantages and limitations of the methods mainly used to support the increase in sympathetic function in insomnia. Collectively, this review aims to provide novel perspectives on conceptualizing insomnia and suggest innovative approaches to help elucidate the relationship between insomnia and autonomic nervous system activity.

1. Introduction

Insomnia is the most commonly reported sleep disorder, with an increasing prevalence recently estimated at 19.2% among middle-age adults (Ford et al., 2015). This prevalence becomes even higher in elderly individuals at up to 50% (Patel et al., 2018). Insomnia disorder is defined as self-reported difficulty with sleep initiation, continuity, quantity, and/or quality, despite sufficient opportunity to sleep, and must be associated with daytime impairment (Edinger et al., 2004). While there is variability in the required frequency and duration of symptoms for clinical diagnosis or research classification, a common definition for chronic insomnia includes symptom occurrence at least three nights per week for at least three months (Sateia, 2014).

Insomnia has deleterious effects on quality of life and overall health status (Zammit et al., 1999), including impaired cognitive function, altered immune function, and of particular emphasis in recent years, increased cardiovascular risk (Sofi et al., 2014; Bhaskar et al., 2016; Javaheri and Redline, 2017; Jarrin et al., 2018). Notably, growing evidence over the past decade has associated insomnia with hypertension, coronary heart disease, and cardiovascular disease mortality (Javaheri and Redline, 2017).

While health consequences of insomnia have been consistently observed, our knowledge on the mechanisms linking insomnia to cardiovascular risk remains incomplete. Many pathophysiological models have centered on the concept of hyperarousal, which consists of a broad range of psychophysiological activation related to dysregulation of central and autonomic nervous system (ANS) function (e.g., sympathetic over-activation) (Bonnet and Arand, 2010; Morin and Benca, 2012; Levenson et al., 2015). In general, these models hypothesize that insomnia is the result of a multisystem dysregulation which promotes wakefulness, thus blocking the occurrence of adequate sleep despite a normal homeostatic sleep drive. Evidence in support of the hyperarousal hypothesis includes findings that individuals with insomnia have heightened indices of cortical activation (e.g., EEG beta activity during sleep), peripheral and central ANS activation (e.g., increased nocturnal cortisol, core body temperature, heart rate, and norepinephrine), and psychological hyperarousal (e.g., racing thoughts at night, anxiety about sleep) (Bonnet and Arand, 2010; Riemann et al., 2010; Levenson et al., 2015). However, these findings have not been consistently replicated. One explanation of the inconsistencies is that in young-middle age populations, chronic insomnia associated with objective measures of short sleep duration (< 6 h) has shown the strongest association with increased risk for cardio-metabolic diseases (Vgontzas et al., 2013). There is also evidence that, not only objective measures of altered sleep quality, but also the severity of subjective sleep complaints correlates with markers of increased autonomic activation (de Zambotti et al., 2013; Xia et al., 2013). As such, both objective and subjective assessments of sleep may provide useful information to predict the biological

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severity of insomnia and its medical impact.

Alterations in ANS activity have gained progressive attention as a specific pathophysiological link between insomnia and cardiometabolic risk (Calandra-Buonaura et al., 2016). In fact, ANS and sleep are tightly coupled and regulated through shared physiological, neurochemical, and anatomical pathways (Cortelli and Lombardi, 2005). Evidence from numerous experimental and epidemiological studies indicates a causal link between several sleep abnormalities (including sleep curtailment, shift work, and sleep disordered breathing) and cardiometabolic diseases. Conversely, sleep disturbances may occur as the consequence of several medical conditions such as obesity, heart failure, and diabetes that are also associated with important ANS changes (Miglis, 2016).

A bidirectional relationship has been proposed, such that 1) the autonomic and cortical activations seen in insomnia sufferers are the result of poor sleep quality (i.e., short sleep duration and sleep fragmentation) (Janackova and Sforza, 2008), and 2) the elevations of physiological parameters indicative of a hyperactive sympathetic nervous system, constitute a state of hyperarousal that predisposes to poor sleep (Bonnet and Arand, 1998; Spiegelhalder et al., 2011; de Zambotti et al., 2013).

Given the central role played by the ANS in the expression of insomnia symptoms (Fig. 1), understanding how ANS changes relate to insomnia phenotypes can help identify their link with increased cardiovascular risk and provide targets for more effective and personalized therapeutic interventions. To this end, comprehensive assessment of ANS function meeting established methodological standards is critical for appropriate interpretation of these complex relationships. Moreover, an understanding of the advantages and limitations involved in each measurement domain further aids interpretation of the existing literature and rationale for novel methodological approaches of future research.

This review aims to summarize and interpret the literature on ANS function in insomnia, with a particular focus on 1) neurophysiological basis of cardiovascular autonomic function, 2) primary findings on ANS assessment in insomnia with integration of new studies not covered in prior reviews, and 3) relevance of findings to better understanding the associations with cardiovascular risk. While chronic insomnia may occur in association with other medical or psychiatric disorders or with substance use, this review focuses on ANS findings related to the independent condition, primary insomnia. For each section, relevant physiology to insomnia and cardiovascular risk will be presented, along with brief overview of key methodologies, which will then be followed by a highlight of studies measuring that particular ANS domain in subjects with insomnia. Collectively, this review aims to generate novel perspectives on conceptualizing insomnia and innovative approaches for subsequent experimental research.

2. Neurophysiological basis of cardiovascular autonomic control

2.1. ANS regulation of blood pressure and heart rate

Blood pressure (BP) and heart rate show circadian and short-term fluctuations resulting from changes in body posture, daily activity, and neurohumoral activity. In particular, the day-night oscillations of BP and heart rate are strongly linked to the sleep-wake circadian rhythm and play a dominant role in the observed 24-h BP and heart rate variations (Smolensky et al., 2007).

Sleep-state transitions also affect BP and heart rate regulation (Somers et al., 1993). Notably, a marked reduction in BP and heart rate, associated with the increase in parasympathetic and reduction in sympathetic activity, occurs during non-rapid eye movement (NREM) sleep, and becomes more pronounced as sleep progresses from stage 1 to slow wave sleep (Mancia, 1993). In contrast, REM sleep is characterized by a marked sympathetic activation associated with BP and heart rate instability, supporting the observation of increased prevalence of cardiovascular events in the early morning hours when transitions to REM sleep are more frequent (Mitler et al., 1988).

Heart rate and BP regulation are differentially regulated by circadian and sleep-related processes. While the diurnal rhythm of heart rate is largely determined by the circadian system, in contrast, BP is strongly influenced by the transition across sleep stages (Trinder et al., 2001). Specifically, BP decreases to its nadir during nighttime sleep, a phenomenon generally referred to as BP dipping (Smolensky et al., 2007). The nighttime BP decrease has major clinical implications, and the loss of normal reduction in BP during sleep (i.e., nondipping status, defined as < 10% decrease in BP during sleep) is considered one of the most sensitive predictors of cardiovascular mortality (Boggia et al., 2007; Banegas et al., 2018).

As a result, conditions associated with poor sleep quality (i.e., sleep fragmentation, increased numbers of arousals, increased amount of wake after sleep onset, reduced amounts of SWS, and altered sleep architecture) are associated with increased sympathetic activity and reduced nocturnal BP dipping (Loredo et al., 2004; Grimaldi et al., 2012). In particular, poor sleepers who display a nondipping BP pattern have been reported to be at high risk to develop hypertension (Yilmaz et al., 2007).

Although not as robust as for BP, evidence has also shown that a blunted heart rate dipping during sleep is a strong independent factor for cardiovascular diseases and for all-cause mortality after adjusting for BP dipping (Ben-Dov et al., 2007).

2.1.1. Blood pressure and heart rate assessment in insomnia

Despite the well-established interaction between sleep and BP

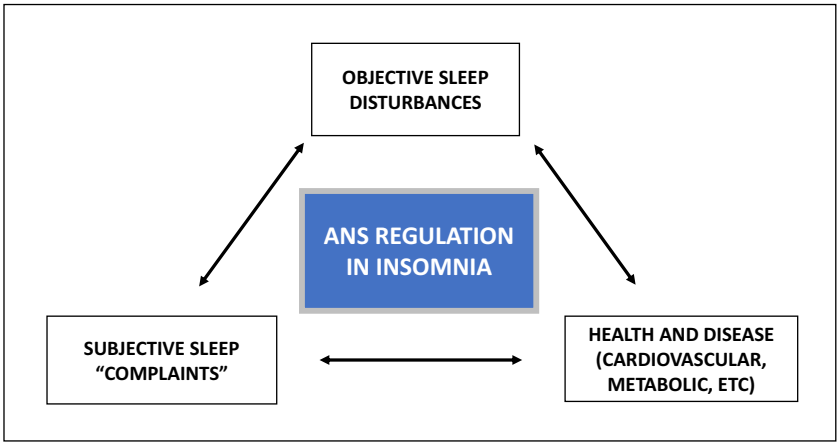

Fig. 1. Schematic representation of the central role played by the autonomic nervous system (ANS) in mediating the complex interaction between subjective and objective sleep disturbances and health outcomes in insomnia.

regulation, along with its relevance for cardiovascular risk, to date this relationship has only been investigated in one study of insomnia patients. Lanfranchi and colleagues (Lanfranchi et al., 2009) used 24-h beat-to-beat BP monitoring to study 13 middle-aged adults with chronic insomnia compared to 13 sex- and age-matched controls. The authors reported an increase in daytime diastolic BP, as well as nocturnal diastolic and systolic BP in subjects with insomnia compared to controls. These changes were associated with a significant reduction in systolic BP day-to-night dipping. These findings were not explained by differences in polysomnography indices of poor sleep. While these results are promising and might constitute a mechanistic pathway to the increased risk for hypertension reported in insomnia sufferers, they need to be replicated. Should they be confirmed, it will be important to determine whether treatments for insomnia can restore the physiological dipping.

Research on insomnia has given more attention to the assessment of heart rate mainly to test the hypothesis that, when compared to good sleeper controls, participants with insomnia would display increased heart rate representative of their hyperarousal status. Unfortunately, there is inconsistency among the studies regarding the period of interest for heart rate assessment (wake, sleep, or both), as well as the condition during which participants were tested (i.e., rest, following a stress test, or both). As a result, the findings have not been unequivocally replicated.

The initial study reporting higher heart rate values in subjects with insomnia vs. controls is from Haynes et al. (1981) who studied 10 young students with "severe" insomnia symptoms at sleep onset and compared them to 11 students identifying as good sleepers. The authors found that resting heart rate measured in the period immediately before lights off was significantly higher in subjects with insomnia compared to controls. However, the increase in heart rate following the exposure to mental stressors during the night was similar in the two groups. Interestingly, opposite findings were observed by a later study from Stepanski et al. (1994), who did not find differences in resting heart rate in a group of 24 young-middle aged adults with insomnia when compared to controls before sleep onset, as well as in the morning after sleep. However, they reported that heart rate was higher in subjects with insomnia during sleep and in the morning after exposure to a performance stress task.

The increase in heart rate during sleep reported by Stepanski et al. (1994) was later replicated by a study in 12 young adults with insomnia compared to 12 controls (Bonnet and Arand, 1998). In contrast, three more recent studies (Varkevisser and Kerkhof, 2005; Jurysta et al., 2009; Spiegelhalder et al., 2011) conducted on young-middle aged adults with insomnia vs. controls did not report differences in heart rate between groups. In one study (Varkevisser and Kerkhof, 2005), participants were examined after 24-h of sleep deprivation, which was expected to enhance their sympathetic activation. However, the authors did not find differences between groups in the pre-ejection period, which is an index of sympathetic cardiac regulation (Berntson et al., 1994). It is also worth noting that in the study from Spiegelhalder et al. (2011), despite that the group with insomnia and controls had similar heart rate values, participants with insomnia displayed a lower wake-to sleep reduction in heart rate, previously indicated as independent risk factor for cardiovascular risk.

A recent review from Dodds et al. (2017) summarizes the overall evidence existing in literature on heart rate findings with insomnia by showing that of 12 studies that assessed heart rate in participants with insomnia, 9 reported non-significant differences when compared to controls. Since the review by Dodds et al. (2017), Carter et al. (2018) reported similar heart rate in young adults with insomnia and controls, both at rest and following a cold pressor test.

Taken together, there is limited evidence of elevated resting heart rate in subjects with insomnia when compared to good sleeper controls. As such, heart rate measures should not be considered a distinctive physiological marker of "hyperarousal" in insomnia.

2.2. Sympathoadrenal activity

The sympathetic nervous system plays a central role in mediating cardiovascular and metabolic adaptations to stress and disease, commonly referred to as the "fight or flight" response. Classically, sympathoadrenal activity is assessed by measuring catecholamines levels, adrenaline and noradrenaline, also called epinephrine and norepinephrine, in plasma or urine (Hjemdahl, 1993).

Epinephrine is the main hormone secreted by the adrenal medulla, and is a major determinant of the stress response. Indeed, epinephrine levels are closely linked to the activation of the hypothalamic-pituitary-adrenocortical system. The low basal levels of epinephrine in the peripheral compartments constitute the main challenge for its measuring.

Norepinephrine is the primary neurotransmitter released by sympathetic nerves. It reaches higher concentrations in plasma and urine that facilitate its measurement, and for this reason it is mainly used as a marker for sympathetic activity in human studies. There are physiological determinants of norepinephrine concentration in both urine and plasma that should be considered to avoid misinterpretation of the results (Hjemdahl, 1993; Grassi and Esler, 1999).

In urine, the 24-h excretion of norepinephrine or its metabolite precursors are usually assessed to infer sympathetic nervous system activity (Kopin, 1985; Esler et al., 1988). There are, however, some limitations to this regard: 1) this approach is strictly dependent on renal function, and 2) it provides a static picture of the sympathetic function, thus is not adequate to assess the acute response of sympathetic system to stress stimuli.

The measurement of norepinephrine in plasma has the advantage to overtake these limitations, but it is still far from optimal in detecting changes in sympathetic activity, particularly in pathological conditions such as hypertension or obesity (Grassi et al., 1995, 1997). The main physiological explanation for this is that plasma norepinephrine levels reflect norepinephrine overflow from all organs (i.e., heart, kidneys, hepatomesenteric region, skeletal muscle and skin), which may vary considerably between and within subjects due to the regionalization of human sympathetic responses. Therefore, a preferred approach to assess sympathetic function, despite the more invasive nature, is the use of regional norepinephrine spillover (Esler, 1993). This method assesses norepinephrine overflow from different organs through the infusion of radiolabeled norepinephrine and its sampling from centrally placed catheters, typically at the heart and kidney. This approach is highly invasive, and has not been applied to sleep research at this point.

2.2.1. Assessments of catecholamines in insomnia

Of the limited studies that have assessed catecholamines in insomnia to characterize sympathetic activity, the majority have measured urinary levels. The initial study is from Vgontzas et al. (1998) who measured 24-h urinary catecholamine over 3 consecutive days in 15 young adults with insomnia and subjective short sleep duration (< 6.5 h). The authors found significant correlations between norepinephrine urinary levels and polysomnography (PSG) indices of sleep disturbances represented by the durations of NREM stage 1 and wake after sleep onset. However, the lack of a control group in this study did not allow determination of whether norepinephrine levels in insomnia are representative of an increased sympathetic tone.

A more recent study from Seelig et al. (2013) reported a significant reduction in 12-h urinary norepinephrine excretion (midnight and early morning) in 13 middle-aged women with insomnia compared to age, sex and BMI-matched controls.

Floam et al. (2015) assessed urinary norepinephrine in the first morning urine void in 29 young adults with insomnia and 19 controls. Despite subjects with insomnia displaying actigraphy-based measures of shorter sleep durations, higher sleep fragmentations and longer periods of wake after sleep onset compared to controls, the authors did not observe differences in norepinephrine levels between the two groups.

Finally, Roehrs and Roth (2016) assessed daytime urinary norepinephrine levels in 95 subjects with insomnia (32 to 64 years-old) at baseline and after 8 months of therapy with zolpidem. The authors reported that participants with higher urinary norepinephrine levels displayed longer sleep latency during a multiple sleep latency test, and showed higher dose escalation of hypnotic self-administrations. These findings have been interpreted as indications of hyperarousal.

To date, one study has assessed plasma norepinephrine in insomnia and found increased levels during sleep in 17 middle-aged adults with insomnia compared to controls (Irwin et al., 2003). Within the insomnia group, norepinephrine levels were positively associated with total sleep time assessed with PSG.

In conclusion, the assessment of catecholamines levels in insomnia has been performed by a limited number of studies, mainly using urine norepinephrine. The different methodological approaches employed (urinary vs plasma measurements), combined with the limitations of peripheral norepinephrine assessment as a reliable and reproducible index of sympathetic nervous system function, likely contribute to the inconclusive results.

2.3. Sympathetic neural activity

In humans, direct recordings of sympathetic nerve activity are obtained using the technique of microneurography. Briefly, this approach requires the insertion of a tungsten microelectrode into a peripheral nerve such as the peroneal, tibial, radial, median, or ulnar nerves (Vallbo et al., 2004; Macefield, 2013; Carter, 2019). Fig. 2 includes a representative tracing of a post-ganglionic muscle sympathetic nerve recording from the peroneal nerve, often referred to as muscle sympathetic nerve activity (MSNA). A recent guidelines paper by Hart et al. (2017) details several key analytical caveats of MSNA, which include quantification of MSNA via burst counts (i.e., burst per minute and burst per 100 heartbeats) or amplitude/area of the burst (i.e., total MSNA).

The use of MSNA is particularly valuable when it is simultaneously collected with beat-by-beat changes in arterial BP through approaches such as finger plethysmography. As demonstrated within Fig. 2, reductions of BP result in a reflex driven increase of MSNA. Likewise, increases in BP are associated with quiescence of MSNA. This classic negative feedback loop, referred to as the arterial baroreflex, is a key homeostatic regulator of BP. While the baroreflex is most relevant to short-term BP control, its role in long-term BP regulation has also been documented (Joyner et al., 2010; Hart et al., 2012).

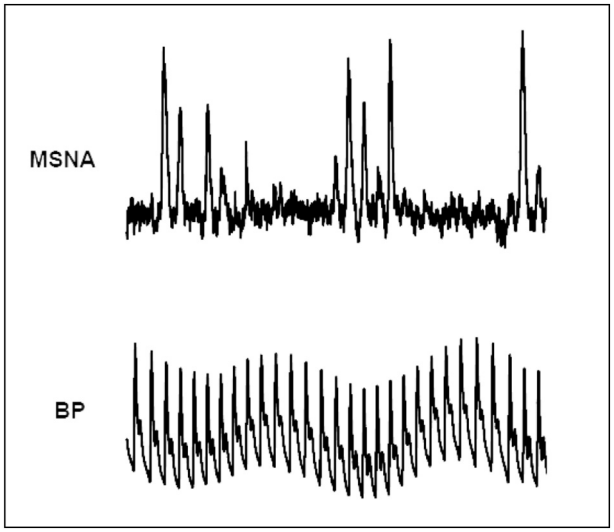

Fig. 2. Representative microneurography recording of muscle sympathetic nerve activity (MSNA) with concurrent recordings of beat-to-beat blood pressure (BP) via finger plethysmography.

A recent review outlines the role of MSNA in several cardiovascular conditions, including hypertension, heart failure, and metabolic syndrome (Carter, 2019). Interestingly, this review also took an objective approach to determining high impact of MSNA studies via number of citations, which revealed that the work by Somers et al. (1995) on subjects with obstructive sleep apnea (OSA) was the most highly cited microneurographic study over the past 50 years. Somers et al. (1995) demonstrated elevated MSNA in subjects with OSA that was reduced by the use of continuous positive airway pressure (CPAP). In addition to OSA, MSNA has also been studied during experimental sleep deprivation. Three studies have consistently reported a reduction of resting MSNA after total sleep deprivation in men (Kato et al., 2000; Ogawa et al., 2003; Carter et al., 2012), and more recent work demonstrates a more sympathoexcitatory state in women (Carter et al., 2012). The reported sex-differences is consistent with epidemiological studies that suggest a stronger relationship between sleep deprivation and hypertension in women when compared to men.

2.3.1. Assessment of MSNA in insomnia

To date, only one study has examined MSNA in subjects with insomnia. Carter et al. (2018) compared resting MSNA, as well as MSNA reactivity to the cold pressor test, in 12 subjects with insomnia and 12 good-sleeper controls. Although resting MSNA was not different between groups, there was a significant difference in sympathetic baroreflex sensitivity and MSNA reactivity. Specifically, sympathetic baroreflex sensitivity was lower in subjects with insomnia, and MSNA reactivity to the cold pressor test was higher in subjects with insomnia. Interestingly, it was the changes in total MSNA that were significantly elevated in subjects with insomnia, suggesting that there may be different sympathetic neural recruiting strategies during stressors in patients with insomnia.

The study by Carter et al. (2018) examined MSNA after morning awakening. While this is typical within most microneurographic studies, in hindsight it might have potentially been more relevant to assess MSNA (as well as MSNA reactivity) during the late evening when patients with insomnia have difficulties initiating/maintaining sleep. It remains possible that resting MSNA is indeed altered in subjects with insomnia in the hours leading up to sleep initiation, but future work is needed to address this definitively.

It is worth noting that insomnia is more commonly reported in women. The study by Carter et al. (2018) was not powered to examine the impact of sex as a key biological variable. However, the vast majority of subjects in both the insomnia and control groups were women. It remains unknown if MSNA responses differ in male vs. female insomnia, but work examining MSNA during total sleep deprivation suggests it might be possible (Carter et al., 2012). Finally, a number of studies suggest that insomnia with objective short sleep duration is the phenotype that is most prone to having a stronger association with hypertension, yet the study by Carter et al. (2018) was not powered to address these sub-types of insomnia. In summary, initial evidence suggests that MSNA reactivity and the sympathetic baroreflex are different in subjects with insomnia when compared to good-sleeper controls, but there is a need to replicate these findings and to more carefully examine factors such as time of day, sex, and objective sleep durations.

2.4. Sympathetic and parasympathetic branches of the autonomic nervous system

The brain regulates cardiac function, BP, respiration as well other visceral activities, in large part, through the sympathetic and parasympathetic branches of the ANS (Benarroch, 1993). More specifically, the homeostatic regulation of cardiac function takes place through the finely modulated cross talk between medullary reflexes activated by baroreceptors, cardiac receptors, and chemoreceptors, as well as the

integrated descending projections to the heart originating from the central autonomic network (CAN) (Benarroch, 1993; Palma and Benarroch, 2014).

The parasympathetic regulation of the heart is mediated by the vagus nerve through the neurotransmitter acetylcholine, whose main effect on the heart is the inhibition of the pacemaker activity of the sinoatrial node with consequent reductions of heart rate, atrial-ventricular conduction and ventricular excitability. The opposite effects are produced by sympathetic innervation of the heart that is mediated by postganglionic neurons releasing norepinephrine (Benarroch, 1993).

The balance between the sympathetic and parasympathetic regulation of the ANS is an important component in the physiological and pathological responses operated by the cardiovascular system. Consistently, the dysregulation between the two branches of the ANS has been implicated in the pathophysiology of several cardiometabolic disorders, and may predict poorer clinical outcomes (Bairey Merz et al., 2015). Thus, methods to assess the cardiac autonomic activity, alone or in combination with brain imaging, have gained particular attention over the years for research purposes, and among them in particular the analysis of heart rate variability (HRV) (Chouchou and Desseilles, 2014).

HRV quantifies the beat-to-beat variability of heart periods (the time intervals between subsequent R waves on the ECG). Spectral analysis of HRV has been extensively used in literature to estimate sympathetic and parasympathetic regulation of the cardiac function. The high frequency component of the power spectrum of HRV (HF: 0.15–0.4 Hz) is considered to reflect parasympathetic activity and vagal respiratory sinus arrhythmia. Conversely, the low frequency component (LF: 0.04–0.15 Hz) reflects the combination of sympathetic and parasympathetic activity. Despite the known limitations of LF component from HRV in assessing the sympathetic component of ANS activity (Eckberg, 1997; Goldstein et al., 2011; Billman, 2013), the LF/HF ratio is often used as an indicator of the sympatho-vagal balance (Shaffer and Ginsberg, 2017).

Since heart rate may be readily and non-invasively assessed, HRV is the most widely used indicator to explore ANS activity during sleep. Changes in HRV have been used to describe the synchronous fluctuation of sleep and ANS activity across the stages of sleep (Mancia, 1993; Tobaldini et al., 2013). The transition from wake to NREM sleep is characterized by a shift towards parasympathetic dominance that is most prominent during slow-wave sleep. This parasympathetic shift is accompanied by a reduction heart rate and BP, and the enhancement of protective factors at the cardiac and vascular level (e.g. decrease in vascular resistance and cardiac work load). During phasic REM sleep, when the presence of rapid eye movements indicates an active dream state, sympathetic activity is predominant; BP, heart rate, and breathing may fluctuate dramatically, and BP and heart rate can be higher than in the waking state.

A robust and reliable measurement of HRV relies on some methodological aspects including controlled environmental conditions, the meticulous selection of the ECG signal included in the analysis to ensure stationary segments, proper sampling frequency, and the assessment of the respiratory frequency (Task Force of The European Society of Cardiology and The North America, 1996). The lack of these components, as often observed in many studies, can account for the lack of reproducibility in findings.

2.4.1. Assessment of sympathetic and parasympathetic activity in insomnia

Bonnet and Arand (1998) were the first to compare HRV in subjects with insomnia and good sleeper controls. The authors reported that the LF/HF ratio was higher in insomnia, suggesting an increase of sympathetic activity. As detailed previously, there is conflicting literature regarding the use of LF/HF as an index of sympathetic activity (Eckberg, 1997; Goldstein et al., 2011; Billman, 2013). In fairness to Bonnet and Arand (1998), this conflicting literature was only beginning to be explored in the late 1990's. Nevertheless, it would seem reasonable to rigorously examine the replicability of the original findings by Bonnet and Arand (1998).

Recently, Dodds et al. (2017) reviewed HRV studies in subjects with insomnia, identifying 16 additional observational studies published after Bonnet and Arand (1998). Dodds et al. (2017) reported that the vast majority (i.e., > 90%) did not report a significant difference in LF/HF in insomnia vs. controls, thus not supporting the hyperarousal theory of insomnia.

In contrast to LF/HF, there is stronger consensus within the field that HF is an appropriate estimate of cardiac parasympathetic activity. Consistent with both the hyperarousal theory and evidence for cardiovascular risk of insomnia, it has often been hypothesized that HF would be lower in subjects with insomnia when compared to controls. For example, de Zambotti et al. (2017) found that women with insomnia symptom onset during menopausal transition were associated with decreased total and HF HRV. Specifically in primary insomnia patients compared to good sleeper controls, Spiegelhalder et al. (2011) observed decreased HF power, most prominently for insomnia patients with objectively determined short sleep duration. Unfortunately, Dodds et al. (2017) reveals that just under 25% of observational studies report a decrease of HF in subjects with insomnia compared to controls. In summary, the majority of evidence suggests that there are not significant differences in HRV between insomnia and good sleeper controls. Coupled with the lack of reproducibility of LF/HF as a surrogate of sympathetic activity, and the limitations and underlying assumptions of HRV in general, there is insufficient evidence to claim HRV data supports the hyperarousal theory of insomnia.

3. Conclusion

A critical appraisal of the existing literature indicates an over-representation of the concept of “hyperarousal” in insomnia that is mainly supported by studies employing methods to assess sympathetic nervous system activity that are easy to access, but are lacking in rigor, reproducibility and specificity (Fig. 3). In particular, the use of HRV has been extensively employed to measure sympathetic/parasympathetic dominance in participants with insomnia. The fact that the majority of these HRV studies yielded negative results, coupled with the intrinsic limitation of this method to provide a robust quantification of sympathetic activity, do not support the hyperarousal hypothesis.

A limited number of studies have measured catecholamines to assess sympathetic activity in insomnia, which represent a more robust parameter than HRV, but the use of inconsistent approaches (i.e., urine vs. plasma) limits both data comparison and interpretation. Finally, the two methods that literature indicates as the most rigorous, reproducible, and specific to quantify sympathetic nervous system activity (i.e. NE spillover and MSNA; Fig. 3) (Esler, 1993; Carter, 2019), have not yet been systematically employed within insomnia research. Carter et al. (2018) reported resting MSNA did not differ in subjects with insomnia compared to controls, but did observe significantly elevated sympathoexcitatory response to a commonly used laboratory stressor, as well as significantly lower sympathetic baroreflex function. Time of day may have impacted the findings as the microneurography was performed upon awakening; future work should consider MSNA prior to initiating sleep. Despite the more invasive nature of microneurography, as well as norepinephrine spillover techniques, they are unique in capturing the heterogeneous and often regionalized responses of the sympathetic nervous system as has been described in both physiological and pathological conditions (Esler, 1993; Carter, 2019). As such, future studies would benefit from inclusion of these measures in order to better elucidate the relationship between insomnia and ANS activity.

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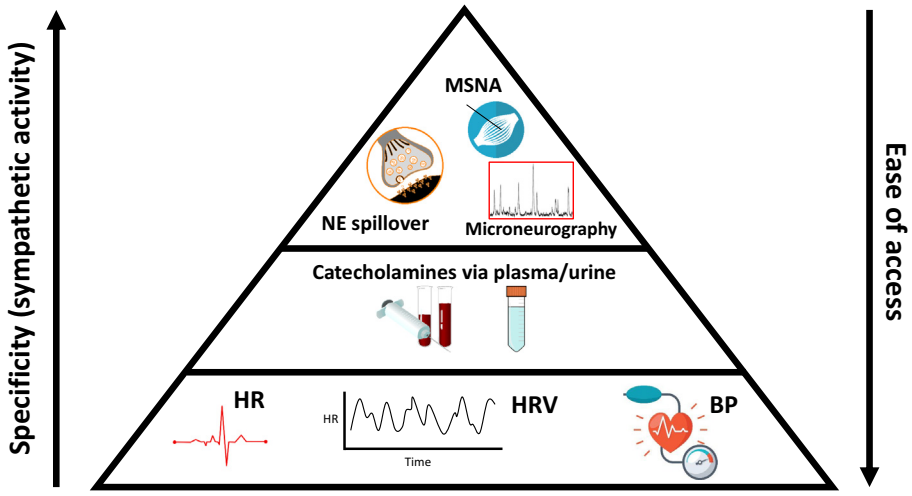

Fig. 3. Schematic drawing illustrating the progression from bottom to top of non-invasive/easily accessible measures of sympathetic nervous function with low specificity/reproducibility towards more specific, but more invasive, approaches. HR: heart rate, HRV: heart rate variability, BP: blood pressure, NE: norepinephrine, MSNA: muscle sympathetic nerve activity.

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