Heart rate variability in insomnia patients: a critical review of the literature.

Kirsty L. Dodds, BHSc [1]

Christopher B. Miller, PhD [2]

Simon D. Kyle, PhD [3]

Nathaniel S. Marshall, PhD [1,2]

Christopher J. Gordon, RN, PhD [1]

[1] Sydney Nursing School, University of Sydney, Australia

[2] NeuroSleep, NHMRC Centre for Research Excellence, Woolcock Institute of Medical Research, University of Sydney, Australia

[3] Nuffield Department of Clinical Neurosciences, Sleep and Circadian Neuroscience Institute, University of Oxford, England, UK

Corresponding author

Christopher J. Gordon

Postal address: Sydney Nursing School, M02 – Sydney Nursing School, The University of Sydney, Sydney, New South Wales, 2006, Australia

Tel: +61 2 9351 0586 Fax: +61 2 9351 0615 Email: christopher.gordon@sydney.edu.au

Summary

Heart rate variability (HRV) is an objective marker that provides insight into autonomic nervous system dynamics. There is conflicting evidence regarding the presence of HRV impairment in insomnia patients. Web-based databases were used to systematically search the literature for all studies that compared the HRV of insomnia patients to controls or reported the HRV of insomnia patients before and after an intervention. 22 relevant papers were identified. Study characteristics were summarised, HRV measures were extracted and a risk of bias assessment for each study was performed. We were limited in our ability to synthesise outcome measures and perform meta-analyses due to considerable differences in patient (and control) selection, study protocols, measurement and processing techniques and outcome reporting. Risk of bias was deemed to be high in the majority of studies. As such, we cannot confirm that HRV is reliably impaired in insomnia patients nor determine the HRV response to interventions. Whilst HRV impairment in insomnia is a widely accepted concept, it is not supported by empirical evidence. Large longitudinal studies incorporating 24-hour recordings are required to elucidate the precise nature of HRV dynamics in insomnia patients.

Key Words

autonomic nervous system, heart rate variability, hyperarousal, insomnia, review

Abbreviations

ECG	electrocardiogram
HF	high frequency power
HFnorm	high frequency power (in normalised units)
HR	heart rate
HRV	heart rate variability
LF	low frequency power
LF/HF	low frequency to high frequency ratio
LFnorm	low frequency power (in normalised units)
NN interval	interval in time between successive normal beats (typically measured from the R wave of a QRS complex)
NREM	non rapid eye movement sleep
pNN50	percent of NN intervals > 50 milliseconds different from previous
PSG	polysomnography
REM	rapid eye movement sleep
RMSSD	root mean square of successive differences of NN intervals for period of interest
RR interval	interval in time between successive R waves (of a QRS complex)
SDANN	standard deviation of the averages of NN intervals in five minute segments of entire recording
SDNN	standard deviation of NN intervals for period of interest

Introduction

Heart rate variability (HRV) describes the variation in time between consecutive heart beats, which is commonly referred to as the RR (R wave to R wave) or NN (normal beat to normal beat) interval. Pacemaker cells located in the sinoatrial node of the heart possess autorhythmicity to maintain heart rate regularity. The heart rate (HR), however, is modulated by a number of physiological factors which alter autonomic nervous system control and increase variability at various frequencies. There are two prominent approaches for quantifying heart rate variation which use spectral or non-spectral techniques to generate HRV measures.

Non-spectral methods involve mathematical derivations of the NN interval. When taken from an electrocardiogram (ECG), this interval is determined by measuring the length in time between consecutive sinoatrial R-wave peaks. As many non-spectral derivations report the HRV in time (milliseconds) or units, they are collectively referred to as time-domain measures. Four time-domain measures are recommended for use by the task force of the European society of cardiology and the North American society of pacing and electrophysiology when assessing HRV to allow estimation of short term (RMSSD), long term (SDANN) and overall HRV (SDNN, HRV triangular index). (1) A description of these HRV measures can be found in Table 1.

Spectral analysis of HRV enables the evaluation of frequency-domain measures. As parasympathetic-mediated changes to HR occur more quickly than sympathetic adjustments, the use of spectral analysis to determine frequency can provide insight into autonomic nervous system dynamics. It has been accepted previously that low frequency (LF) activity is a correlate of parasympathetic and sympathetic activity whilst high frequency (HF) activity reflects parasympathetic activity only. As such the ratio between these (the LF/HF ratio) provides an estimate of sympathovagal balance which is the putative equilibrium of the sympathetic and parasympathetic systems. However, the

physiological significance of the lower frequency bands (including LF and the LF/HF ratio) is now contested and caution is required when interpreting these measures. (2-4) This is further summarised in Table 1. For a more detailed explanation of the physiological correlates of HRV measures refer to the previous review of Stein and Pu (5).

Insert Table 1 about here

Heart rate variability recordings are employed in a vast range of settings, popular due to the non-invasive collection methods. The clinical utility of HRV was realised in the late 1980s when decreased HRV, defined by a reduction in 24-hour SDNN, was found to be a strong predictor of mortality post myocardial infarct. (6) HRV has since been used to investigate both healthy and disease states in clinical and research settings.

The incorporation of HRV analysis during sleep has been a logical extension as the ECG is a component of overnight polysomnography (PSG). This has acted as a catalyst for further examination on the bidirectional relationship between autonomic nervous system activity and sleep physiology. (7) As such, it is not surprising that time and frequency-domain HRV measures, primarily from short recordings (i.e. less than 24 hours), are increasingly being reported in the sleep literature.

It is now known that HRV has circadian periodicity, significant alterations during the transition from wake to sleep and across sleep cycles. (8, 9) Although there are limited studies with comparable measures, Bonnemeier *et al.* (10) and Li *et al.* (11) have shown that vagal HRV measures follow a day-night pattern increasing during the night. (12) Importantly, these are correlated with age and sex. (10, 11) It is also known that there is a shift in sympathovagal balance between non rapid eye movement (NREM) and rapid eye movement (REM) sleep. (5, 9, 13) Accordingly, the research focus

has shifted to investigating the associations between HRV, sleep disorders and their subsequent comorbidities and the incorporation of non-traditional HRV techniques. (5, 13, 14)

Given the interplay between HRV and cardiac autonomic activity, the use of HRV in insomnia research may assist further investigation into the pathophysiology and potential health impacts of insomnia. Hyperarousal has been defined as 'a state of increased arousal at the physiological, cortical, cognitive or emotional level' (15) and hypothesised to contribute to the development, maintenance and 24-hour systemic sequelae of insomnia. (16) As such, the notion of physiological hyperarousal has been investigated by measuring HRV in insomnia patients despite the uncertain relationship between autonomic dysfunction, insomnia and cardiovascular disease. (16)

With an estimated worldwide prevalence of 10%, insomnia is the most common sleep disorder. (15, 17, 18) Clinical diagnosis in accordance with the most recent diagnostic and statistical manual of mental disorders requires the patient to report difficulty initiating and/or maintaining sleep with subsequent daytime impairments greater than three nights per week and for at least three months. (19) Insomnia patients also have increased medical and psychological comorbidities. (15)

Heart rate variability studies of the insomnia population have increased since 1998 after the influential work of Bonnet and Arand (20) which was supportive of the hyperarousal theory. This study revealed altered sympathovagal balance in patients with insomnia compared to controls. (20) However, the extant research literature has not been able to replicate these findings with comparable detail and instead yielded somewhat inconsistent, divergent findings. (21)

Whilst two reviews examining HRV, sleep and sleep disorders have been published previously they did not systematically synthesise the findings of the insomnia – HRV literature and we were aware of additional studies that were not included (5, 13). Therefore, the aim of this review was to identify all

insomnia related research studies using HRV to determine if HRV was impaired in adult patients with

insomnia and whether interventions alter HRV.

Methods

We undertook an extensive search of the literature using CINAHL, EMBASE, Google Scholar, PubMed, Scopus and Web of Science databases on 25th January 2016. Where possible the search incorporated a subject heading and key word strategy, combining "heart rate variability" or "HRV" and "insomnia". The systematic search strategy was modified as necessary according to the database being searched, as shown in Appendix A. No limitations were used with the exception of Google Scholar where restrictions were used to exclude patents and citations. We had two main questions: 1) whether there were any differences in HRV of insomnia patients compared to controls (observational) and 2) whether treatment interventions resulted in changes to the HRV of insomnia patients (interventional).

In order to be included for review, studies required the following:

1) Participants – humans ≥ 18 years old (observational) or insomnia patients (interventional)

2) Exposure – diagnosed with insomnia (observational) or a treatment for insomnia (interventional)

3) Comparisons – controls who were deemed to be good sleepers (observational) or the same group of patients compared before and after treatment or an ineffective or placebo treatment (interventional)

4) Outcomes – standard time and/or frequency-domain HRV measures with recordings of any length at any time during sleep and/or wake

5) Study design – case-control studies, observational cohort and cross-sectional studies (observational) and randomised controlled trials, non-randomised controlled trials and uncontrolled trials (before and after studies; interventional).

We included research studies that incorporated HRV measurements as either primary or secondary outcomes. Case studies and publications without original data were excluded from the review. The

interventional studies were not restricted to validated insomnia treatments, but rather any interventions that were conducted in insomnia patients and included pre- and post HRV measurements.

On completion of the database searches, duplicates were removed. All remaining studies were reviewed for eligibility by one author (KD) using the study title, abstract and, when required, full text. The reference lists of remaining publications and the bibliographies of relevant review articles were also searched for grey literature and otherwise missed publications.

Study measures were collected through the use of tables that identified study characteristics and standard time and frequency-domain HRV measures. Several tools were used by one author (KD) to assist with assessing the risk of bias within studies. Case-control studies were evaluated using a modified version of the national institute for health and care excellence methodology checklist. (22) This checklist assisted in reviewing studies for internal validity by methodically appraising the selection of cases and controls, confounding factors and statistical methods. (22) Intervention studies were evaluated using the cochrane collaboration's tool for assessing risk of bias. Designed for randomised controlled studies, this helped us to scrutinise the studies for selection, performance, detection, attrition or reporting bias. (23)

Findings

SEARCH PROCESS

The database search yielded 555 records (CINAHL 9, EMBASE 182, Google Scholar 21, PubMed 60, Scopus 140, Web of Science 143). After removal of duplicates, 275 publications remained and of these 22 met the inclusion criteria. No additional publications were identified after a manual search of the reference lists. There were 17 case-control studies (20, 21, 24-38), one of which was a nested case-control study from a larger cohort. (34) We did not identify any cohort or cross-sectional study designs. Five research studies compared insomnia patients before and after an intervention. The types of interventions were cognitive behavioural therapy for insomnia (39), pharmacotherapy (gabapentin) (40), acupuncture (41), acupressure (42) and paced breathing (43). There were no randomised controlled trials. A diagrammatic schema of the search results is shown in Figure 1.

Insert Figure 1 about here

OBSERVATIONAL STUDIES

Demographics

Participant numbers and demographics of the observational studies are presented in Table 2. The sample size of patients ranged from 8 to 85 (with 8 to 55 controls respectively). (27, 29) Three studies exclusively involved female participants (33, 34, 36) and one study involved only males (32). Bonnet and Arand (20) did not report the sex-ratio of their study participants (20). The age of participants was also variable with the average patient age ranging from 23.0 (SD 2.4) to 53.2 (SD 13.6) years. In accordance with the time span of included studies, the majority of studies involved patients diagnosed according to the fourth edition of the diagnostic and statistical manual of mental disorders. (21, 26-28, 30-33, 35, 36, 44) In contrast, Varkevisser *et al.* (37) and Farina *et al.* (29) utilised the international classification of sleep disorders, whilst two other studies used the research diagnostic criteria for primary insomnia, which set the benchmark at the time of publication. Finally,

there were two studies that utilised non-standard criterion based upon a combination of subjective symptomology and arbitrary PSG criteria, incorporating sleep efficiency and/or sleep onset latency. (20, 34)

Data collection

Most night time HRV data collection was performed in the sleep laboratory, with the exception of four studies that included testing in participants' homes or an alternative health care facility. (29, 34, 36, 44) As shown in Table 2, HR data collection was achieved through the use of Holter monitors, heart monitor belts and PSG-based ECGs, resulting in sampling rates ranging from 125 to 1024 Hz. (30, 34, 36)

HRV measures

It was difficult to synthesise the findings of HRV measures reported in the observational studies. Total power (TP) was the only HRV measure that provided unequivocal findings across observational studies - no significant differences were reported between insomnia patients and controls (Table 3). The second most consistent finding was that mean HR was found to be higher in insomnia patients compared to controls (20, 26, 27, 29, 33, 44); nevertheless, others reported no significant group differences in this measure between insomnia and controls (21, 24, 31, 33, 37). Cellini *et al.* (24) found HFnorm decreased compared to eight others who reported no significant differences. Both Bonnet and Arand (20) and Farina *et al.* (29) found the LF/HF ratio to be increased in insomnia patients compared to controls although 11 other studies did not show this response.

The classic findings of increased sympathetic-related measures of LF and the LF/HF ratio with a reciprocal reduction in parasympathetic measures of RRI, SDNN and HF (20) in insomnia patients compared to controls has not been replicated comprehensively. Four studies have corroborated some of these findings but not across all HRV measures and sleep stages. (21, 29, 31, 44) We were

not able to identify any other study with HRV outcome measures suggestive of both increased sympathetic and decreased parasympathetic activity which has been reported to strongly support the autonomic dysfunction and evidence of physiological hyperarousal. (45, 46) Table 3 provides an overview of the HRV outcomes of the case-control studies.

Sleep onset (SO)

Heart rate variability activity during the transition from wakefulness to sleep is of particular interest given the changes in autonomic activity and the reported heightened symptomatology in insomnia patients at this time. (47) We identified two studies that measured HRV during the SO period (25), (33) and one that compared pre-, and post-sleep HRV measurements (21). de Zambotti *et al*. (25) found greater wake to sleep increases in HFnu which (matched by a greater wake to sleep HR reduction) in insomnia patients compared to controls, suggesting a greater increase in vagal control during the SO process. Maes *et al*. (33) did not find any significant differences between insomnia patients and controls preceding SO in either HR or HRV parameters. Although not specifically related to the SO process, Spiegelhalder *et al*. (21) found a group by stage interaction indicating a dampened HR reduction from wake to (N2) sleep, possibly reflective of subtle nuances in autonomic dynamics.

Daytime only

Daytime HRV testing of insomnia patients was undertaken in four studies with contradictory results. Fang *et al.* (28) reported no significant differences in four frequency-domain HRV measures (TP, LF, HF, LF/HF), whereas Cellini *et al*. (24) reported an increase in sympathetic activity (based upon impedance cardiography) together with decreased HFnorm, correlating with parasympathetic activity in insomnia patients. Two of the daytime HRV studies involved a physiological challenge – baroreflex sensitivity and postural change. Despite differences in the physiological perturbation, one study did not find any group differences (35), whilst the other reported insomnia patients to have attenuated or absent HRV responses to postural change. (31)

Extended recordings

We could only identify three studies whereby participants undertook extended HRV recordings. In a constant routine protocol whereby participants remained awake and in a semi recumbent position across 24 hours, Varkevisser *et al.* (37) did not find any between-group differences in HR or RMSSD. Both Yang *et al.* (44) and Farina *et al.* (29) utilised 24-hour recordings but did not report 24-hour HRV outcomes.

Risk of bias

Risk of bias of the observational studies is presented in Table 4. There was considerable bias in many studies, with six studies not taking cases from the same population as controls. (21, 29, 33-35, 37) This was evident in the absence of a consistent methodology to match cases to controls in Table 2. The selection of controls was problematic with many not abiding to the suggested research diagnostic criteria for selection of insomnia controls. (48) Potential confounders, such as age, sex and comorbidities, were not often included despite the known impact upon HRV. The wide age range between studies is evident in Table 2. The age range was also significant within studies, as was highlighted by Spiegelhalder et al. (21) in their secondary analysis using covariates which found that age significantly impacted on both time and frequency-domain HRV measures including SDNN, RMSSD, pNN50, HF and the LF/HF ratio whilst sex affected the time-domain measures of SDNN, RMSSD, pNN50. Despite this, to the best of our knowledge no studies included in our review specifically analysed sex x group interactions. Finally, none of the studies reviewed accounted for the additional confounders of menstrual cycle phase and/or women's reproductive stage. (49)

Insert Table 2, 3 & 4 about here

INTERVENTIONAL STUDIES

Demographics and data inclusion

All intervention studies were open label, single-arm clinical trials. Participant numbers were mostly small with the largest sample size of 31 patients. (42) The diverse age range is evident in Table 5. Between the five studies, four different diagnostic methods were used for classification of insomnia. Insomnia severity of patients across studies was not able to be compared as one study provided scores for the insomnia severity index (39), two for the Athens insomnia scale (41, 42) and two for the Pittsburgh sleep quality index (known to measure sleep quality, not insomnia symptoms) (40, 43). The longest follow-up time post intervention cessation was eight weeks post-therapy. (39-42, 50) As with the observational studies, there was no uniformity in data capture and analysis methods, with the exception of the acupuncture and acupressure intervention studies as these were performed by the same research group. (41, 42)

HRV measures

All interventions evoked some change in at least one HRV measure in insomnia patients (Table 6). Both acupuncture and acupressure caused stimulation-dependent changes in HRV. Cognitive behavioural therapy (CBT), gabapentin and acupuncture interventions were associated with an increase in parasympathetic activity (pNN50 and HF respectively). Heart rate variability measures that may represent sympathetic activity were reduced after gabapentin (decreased LF, LFnorm and LF/HF ratio) and CBT responders (decreased LF). Interestingly, four (of the five) interventions resulted in TP augmentation which contrasted with findings from the observational studies which found this HRV measure to be equivalent in insomnia patients and controls.

Risk of bias

No randomised control trials of the HRV of insomnia patients were identified. Therefore, no interventional studies achieved random sequence generation, (for the intervention) or undertook

blinding of participants or study personnel. The possibility of selective reporting was present in all types of studies. Due to the absence of prospective clinical trial registration we could not ascertain whether any outcome switching has occurred except inside the research groups that have maintained their HRV variable list. It was not clear why only some HRV measures were used and if all HRV findings were reported. Statistical under-powering of small studies must also be allowed for when considering the results. Risk of bias assessment for interventional studies is presented in Table 7.

Insert Table 5, 6 & 7 about here

ALL STUDIES

Technical considerations

Across all studies there was a wide range of data cleaning and processing methods. Some authors used fully automated programs whilst others performed visual inspection of the R wave detection and manual editing for correction when required. There was discrepancy in the handling of HRV time periods that included artifact, sleep-related arousals and/or multiple sleep stages. Not surprisingly, a range of statistical methods were applied, with some but not all studies choosing to normalise the HRV measures. (21, 24-27, 32, 34, 35)

Time of HRV recording

The HRV outcomes that were reported in Table 3 and Table 6 demonstrate a variety of different collection periods. Heart rate variability measurements were taken from participants in wake and/or sleep. Furthermore, sleep-related HRV measures were from various sleep stages, aggregates of sleep stages (e.g. NREM sleep combined), sleep cycles (e.g. early NREM vs late NREM) or time periods (e.g.

sleep onset). For example, whilst both Bonnet and Arand (20) and Farina *et al*. (29) reported an

increase in the LF/HF ratio in insomnia patients compared to controls, Bonnet and Arand (20)

reported this measure to be increased during stage one, two and REM whereas Farina *et al.* (29)

found this only in early N2. This made direct comparison between studies difficult.

Discussion

There are numerous reports in the literature that HRV is impaired in insomnia patients. These typically draw heavily on the findings of a small number of observational HRV research studies. (20, 21) These case-control studies have reported a decrease in some HRV measures related to parasympathetic activity in insomnia patients during sleep and these HRV impairments have been used to support a putative causal pathway for physiological hyperarousal and insomnia. (51) This would be a logical inference; however, it is challenging to draw firm conclusions from the studies in our review, with nearly half of the observational studies reporting no significant HRV difference between insomnia patients and controls. In addition, HRV was measured during a multitude of different states (wake, sleep onset, sleep stages, post-sleep wake), with a lack of consistent findings across studies. When between-group differences were evident, they were often in dissimilar time and frequency-domain HRV measures and not replicated consistently in other studies. Furthermore, there appears to be insufficient evidence to determine if HRV in insomnia patients is impaired during the day or how it may vary across the 24-hour cycle. We therefore suggest that the evidence for HRV impairment in insomnia is imperfect and that further studies are required.

There were only five intervention studies and as these modalities were not synonymous it was difficult to draw any conclusions from the data. Only one study examined HRV before and after the gold-standard treatment for insomnia, cognitive behavioural therapy and this was in a modest sample of 26 patients. (52-56) Interestingly, despite a uniform increase in HR in insomnia patients in some but not all case-control studies (refer to Table 3), HR was only lowered during stimulation by acupressure and acupuncture. Conversely, whilst there was no difference in TP when comparing insomnia patients to controls, it was the HRV measure that showed the most consistent change, with four (of five) interventions provoking increased TP. Accordingly, the interventions used in the studies from this review do not appear to consistently affect the HRV dynamics of insomnia patients. This

may be related to the intervention modality, for instance, ear accupressure was unlikely to affect insomnia severity. (42) Moreover, there was a lack of CBT studies which several meta-analyses have shown to be efficacious. (52-56) Therefore, the impact of interventions on HRV autonomic characteristics in insomnia patients needs further investigation using well-designed randomised controlled trials to mitigate bias and enhance the clinical application of the findings.

Highly disparate populations were investigated across the studies in our review. In many studies cases and controls were retrospectively selected and despite providing statistical comparison between the groups, there was a lack of case-match methodology reporting. Sample sizes were generally small across all studies which limited the generalisability of the findings. The largest of the studies reviewed had 85 cases and 55 controls, derived from non-comparable populations. (29) It is likely that many studies were underpowered and this may have impacted on the findings.

Several diagnostic methods and insomnia severity scales were used, making it difficult to compare populations between studies. An example of this is the use of sleep efficiency for insomnia patient eligibility. Whilst two studies only included insomnia patients when PSG sleep efficiency was 85% or less, others included insomnia patients with high sleep efficiency values 90% (SD 4) and 91% (SD 5) respectively. (20, 26, 27, 34) Only one study classified the severe insomnia phenotype of total sleep time less than 6 hours. (45) This study quantified short-sleep duration insomnia using PSG-derived sleep efficiency percentage, whereby those with a sleep efficiency of less than 85 were considered to be short-sleepers. This subgroup analysis revealed differences between short-sleeping insomniacs and controls (refer to Table 3). However, no within-group comparisons were made between these insomnia patients i.e. short sleep duration insomnia patients and those with a longer sleep time. Although it was not the focus of our current review, we are not aware of any other research that has been published that has used HRV to phenotype insomnia patients.

Sex, sex-ratio and age of participants and controls were diverse. This is of particular concern given the known influence imparted on HRV by sex and/or age. (57, 58) Evidence from a recent meta-analysis found females to have both higher mean HR and greater vagal activity evident in a number of HRV measures. (58) It must be noted that the authors of this meta-analysis also deduced that 'mean heart rate alone provides little to no insight into risk for cardiovascular disease'. (58) Researchers should also be mindful of possible HRV implications from co-morbid sleep disorders (particularly sleep obstructive sleep apnoea) when designing and reviewing studies particularly given the possible impact that these have on HRV. (5, 59) Other potential confounders such as stimulants, medications and medical comorbidities were often unreported and may have influenced the HRV findings.

Considering the tremendous amount of inter-individual variability already present in HRV measures, methodological considerations for HRV analysis are of utmost importance. (60) Standards for the measurement and physiological interpretation were developed in 1996 by the task force of the European society of cardiology and the North American society of pacing and electrophysiology, with further recommendations on the use of novel HRV techniques in the 2015 position statement. (1, 14) Despite stating that '…the complete signal should be carefully edited using visual checks and manual corrections of individual RR intervals and QRS complex classifications', many insomnia-HRV studies have not used these standards. (1) Notably, only four case-control studies (21, 28, 29, 32) and three interventional studies (39, 40, 50) referenced the task force guidelines when describing methodology. Erroneous HRV results may have arisen from physiological artifact (such as ectopic heart beats), technical methods or the algorithms used for R wave detection and editing. Signal length and discontinuity can also easily affect power spectral analysis, obscuring HRV findings. (61) Quintana et al. (62) have recently published guidelines for reporting HRV in psychiatry, specifically outlining the different aspects required when reporting HR collection, RR interval analysis, cleaning methods and HRV calculation techniques. For researchers examining HRV during sleep, a number of

additional difficulties including but not limited to the inherent autonomic changes evident in different sleep stages, circadian effect, the influence of comorbid sleep disorders, variable recording lengths and the inability to control respiratory rate need to be considered. Until such clarification is provided, researchers should report all aspects of their study protocol, participant demographics, analysis techniques and HRV findings.

In further attempts to elucidate the presence of physiological arousal amongst insomnia patients and provide greater understanding into the sleep and nocturnal physiology of insomnia patients, a number of researchers have extended the scope of their HRV research to include additional measures such as EEG parameters. In a sample of 28 males, Jurysta and colleagues (32) found 14 insomnia patients to have decreased coherence between HF HRV power and delta EEG power when compared to 14 controls despite having similar HRV values. Research by Maes (33) utilised HRV together with EEG measures including K complexes and sleep spindles whilst Rothenberger (36) measured the degree of correlation between HF-HRV and delta EEG during sleep in 197 women. Whilst all studies found some degree of altered associations between HRV and EEG in insomnia patients compared to controls, it remains unclear whether this is a trait of insomnia patients or a consequence of the disorder.

Limitations of our review include the use of two different risk of bias assessment tools and this was performed by one author only. No attempts were made to contact study authors when method of HRV analysis was unclear. We were unable to perform a meta-analysis due to the difficulty collating findings arising from studies of different designs, study populations, measurement techniques and analyses.

A number of studies in this review have drawn conclusions about the associations between physiological hyperarousal, HRV and cardiovascular disease, often in reference to the study results. It is tempting to deduce that an increase in sympathetic-related HRV measures will be mirrored by a decrease in parasympathetic-related HRV measures and that this explains the autonomic dysfunction. However, the traditional notion of an antagonistic autonomic nervous system is now questioned. (63) Whilst the initial HRV and insomnia research of Bonnet and Arand (20) described an increase in sympathetic and decrease in parasympathetic activity across all reported sleep stages, this small study has not been replicated consistently in the past 18 years. The additional questioning of the correlation between LF and LF/HF with sympathetic activity makes it unlikely that HRV alone can assist in determining potential causal pathways between autonomic dysfunction and cardiovascular morbidity in the insomnia population. Certainly the findings from this review cannot support this link.

Future research should employ 24-hour HRV recordings. The influence of sleep stages and HRV recordings needs to be clarified. Many of the studies in this review did not report all HRV across sleep stages and this limited our ability to meta-analytical approach. Reporting of all HRV recorded across sleep stages should be included to facilitate cross-comparison of studies. Previous cardiovascular studies have shown associations with impaired HRV in 24-hour and mortality and morbidity and whilst this does not demonstrate causality, it would provide evidence of a link between physiological hyperarousal in insomnia and cardiovascular risk. Moreover, the influence of known confounders, such as age and sex, must be included in future analyses.

In conclusion, our critical review of the insomnia-HRV research studies revealed varied results and a lack of consistent HRV findings in insomnia patients. We suggest that longitudinal studies using repeat measures with large sample sizes are required to determine the relationship, if present, between HRV and insomnia.

Practice Points

1) There is inconsistent evidence to suggest that heart rate variability is impaired in insomnia.

2) We cannot deduce if or how insomnia interventions alter heart rate variability and autonomic dysfunction.

3) Measurements from short-term heart rate recordings cannot be compared to 24-hour recordings, thus the use of heart rate variability as a prognostic tool for cardiovascular disease in insomnia patients is not yet possible.

Research Agenda

1) Develop recommendations for the measurement, analysis and reporting of HRV in in sleep and circadian research in order to aid interpretation, reproducibility and cross-comparison.

2) Perform large longitudinal studies of insomnia patients and controls that incorporate 24-hour recordings to determine the heart rate variability of insomnia patients across the sleep-wake cycle.

3) Consider the retrospective and prospective validation of the cardiovascular disease predictive power of heart rate variability measures in insomnia patients and appropriately matched controls (possibly via a nested case-control study within a large cardiovascular disease cohort study).

4) Explore whether heart rate variability can be used to phenotype the heterogeneous insomnia population.

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APPENDIX A

Boolean search strategy for each database.

Search performed on 25th January 2016

No limitations on publication date, type or language

CINAHL - 9 results

(MH "Heart Rate Variability" OR "heart rate variability" or HRV) AND (MH "Insomnia" OR insomnia*)

Embase – 182 results

(hrv OR 'heart rate variability'/exp OR 'heart rate variability') AND insomni*

Google Scholar - 21 results

Did not search for patents or citations

(intitle:"heart rate variability" OR intitle:HRV) AND (intitle:insomnia OR intitle:insomniac OR intitle:insomniacs)

Pubmed - 60 results

HRV or "heart rate variability" AND insomni*

Scopus – 140 results

(hrv OR "heart rate variability") AND insomni*

Web of Science - 143 results

(HRV or "heart rate variability") AND insomni*