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ORIGINAL RESEARCH

Heart rate phenotypes and clinical correlates in a large cohort of adults without sleep apnea

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Background: Normal sleep is associated with typical physiological changes in both the central and autonomic nervous systems. In particular, nocturnal blood pressure dipping has emerged as a strong marker of normal sleep physiology, whereas the absence of dipping or reverse dipping has been associated with cardiovascular risk. However, nocturnal blood pressure is not measured commonly in clinical practice. Heart rate (HR) dipping in sleep may be a similar important marker and is measured routinely in at-home and in-laboratory sleep testing.

Methods: We performed a retrospective cross-sectional analysis of diagnostic polysomnography in a clinically heterogeneous cohort of n=1047 adults without sleep apnea.

Results: We found that almost half of the cohort showed an increased HR in stable nonrapid eye movement sleep (NREM) compared to wake, while only 13.5% showed a reduced NREM HR of at least 10% relative to wake. The strongest correlates of HR dipping were younger age and male sex, whereas the periodic limb movement index (PLMI), sleep quality, and Epworth Sleepiness Scale (ESS) scores were not correlated with HR dipping. PLMI was however significantly correlated with metrics of impaired HR variability (HRV): increased low-frequency power and reduced high-frequency power. HRV metrics were unrelated to sleep quality or the ESS value. Following the work of Vgontzas et al, we also analyzed the sub-cohort with insomnia symptoms and short objective sleep duration. Interestingly, the sleep–wake stage-specific HR values depended upon insomnia symptoms more than sleep duration.

Conclusion: While our work demonstrates heterogeneity in cardiac metrics (HR and HRV), the population analysis suggests that pathological signatures of HR (nondipping and elevation) are common even in this cohort selected for the absence of sleep apnea. Future prospective work in clinical populations will further inform risk stratification and set the stage for testing interventions.

Keywords: heart rate variability, insomnia, sleepiness, sleep quality, periodic limb movements

Introduction

Normal sleep is associated with typical physiological changes of the central nervous system, the standard description of which is sleep staging as defined largely via electroencephalography (EEG) sensors. The autonomic nervous system, typically interrogated via the electrocardiography (ECG) signals, also undergoes marked changes in normal sleep vs wake, in rapid eye movement (REM) sleep vs nonrapid eye movement sleep (NREM) sleep, and in disease states.[1–3] However, in clinical practice, the sleep phenotype is described mainly according to the staging, obstructive sleep apnea (OSA) metrics, and periodic limb movements in sleep (PLMS), while the ECG and basic heart rate (HR) data are mainly evaluated manually for evidence of arrhythmia.

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Extensive evidence suggests that cardiovascular metrics carry potentially important information about sleep physiology and pathophysiology, as well as systemic cardiovascular risk. For example, the autonomic stability of slow wave NREM sleep has been linked to blood pressure dipping.[4,5] The absence of normal nocturnal blood pressure dipping has been implicated in the cardiovascular risk of patients with hypertension (HTN),[6] sleep apnea,[7,8] normotensive chronic insomnia,[9] and sleep fragmentation.[10,11] Furthermore, blood pressure nondipping has been associated with increased mortality.[12–14] Although routine clinical sleep monitoring does not currently include blood pressure measurement, analysis of cardiac physiology has been extensively performed in hopes of characterizing sleep quality, including HR variability (HRV) and cardiopulmonary coupling.[1,2,15]

While nocturnal blood pressure monitoring is not standard in polysomnography (PSG) recordings or sleep disorder evaluations, HR and ECG are routinely measured. Certain cardiac metrics may have vascular prognostic value, as well as phenotyping of insomnia,[16,17] sleep apnea,[18–20] and PLMS.[21–23] Drawing a parallel with nocturnal blood pressure dipping, several reports of HR dipping during sleep suggest that lack of dipping is associated with adverse cardiovascular outcomes, including elevated mortality risk over a long-term horizon[24–26] and after acute myocardial infarction[27] (although some cohorts only showed increased noncardiovascular mortality[28,29]). HRV, likewise, has been associated with adverse cardiovascular outcomes and mortality.[30,31] The relationship of HRV metrics with underlying autonomic physiology is often summarized as the high-frequency (HF) component reflecting the respiratory-driven time scale and predominantly parasympathetic influences, while the low-frequency (LF) component reflects a combination of sympathetic and parasympathetic factors.[2] However, it has been argued that this is an oversimplified view[32] and also that HRV itself depends strongly on HR.[33]

We performed a retrospective exploratory study to investigate the relationship of HR and HRV metrics with a variety of clinical features in a large cohort (n=1047 adults without sleep apnea) of clinical PSG data from our center. We specifically excluded OSA because it is well known to cause a multitude of physiological changes, including blunted or reverse blood pressure dipping.[8,34] We specifically sought to investigate correlates of PLMS, sleepiness, sleep quality, and misperception. These variables are available in cross-sectional analysis; lacking outcome measures of a longitudinal study, we cannot use the cardiac metrics to test hypotheses related to clinically relevant outcomes currently.

Methods

The Institutional Review Board of the Partners Human Research Committee approved the retrospective analysis of our clinical sleep laboratory database without requiring additional consent (criteria including minimal-risk of the analysis, waiving consent would not compromise the welfare of patients, and the impracticality of the research without waiving consent). Only de-identified data contributed to the analysis. This study involved diagnostic PSGs performed on adults in our clinical sleep laboratory, for any indication; patients undergoing positive airway pressure treatment were not included. Although most referrals to our center are for the evaluation of OSA, this cohort was selected based on the absence of OSA, defined as follows: the apnea–hypopnea index was <5 (using a 4% threshold definition of desaturation of SpO_2 for scoring hypopneas) and the respiratory disturbance index (RDI) was <10, where the RDI includes nonhypoxic events that were associated with EEG arousal. Of n=1089 initial PSG extractions, we excluded n=16 for a prespecified minimum total sleep time (TST) of 2 hours and we also excluded a small number with either technical problems with the scoring file (n=20) or because of the presence of a pacemaker (n=6). None of the subjects had atrial fibrillation on manual review. There were no other exclusions applied. The total cohort for analysis is thus n=1047. PSG was performed according to American Academy of Sleep Medicine standards (2007 rules) and scored by experienced registered technologists. PSGs were recorded with the same system (Grass/Twin; Natus Medical Incorporated, Pleasanton, CA, USA), in the time frame of 2009–2015. Single-lead ECG was obtained from location V2 and sampled at 200 Hz.

HR analysis was performed on the signal output of the pulse oximeter, which is a moving average window of detected beats, such that instantaneous changes are smoothed, but overall trends are preserved. The mean HR values using ECG or HR methods were not statistically different in any sleep–wake stage. We used this signal to calculate the slope values for stable blocks of each stage (defined as at least 5 minutes of continuity within any given sleep–wake stage), using custom MATLAB code (The MathWorks Inc, Natick, MA, USA). We excluded unstable bouts (<5 minutes of continuity for any stage) because we reasoned that transitions and the accompanying arousals would be more likely to confound the HR measures with noise related to arousals and movement. The mean HR values for unstable bouts were within ~1 beat per minute (bpm) of the equivalent stable bout means (data not shown). Clock time was not considered (in other words, we combined analysis across all

available recordings, typically between 10 pm and 6 am) or were REM–NREM cycles considered separately. Wake bouts were not limited to the sleep onset period; any stable block of wake was accepted for analysis.

The HRV analysis was performed on the single-lead ECG channel from each PSG. The algorithm was implemented in MATLAB. The RR interval from autoidentified QRS complexes yields the beat-to-beat (instantaneous) HR intervals. Missing, ectopic beats, and artifact segments were corrected using a spline cubic interpolation as suggested in the HRV guidelines.[35] The resulting R-R intervals were resampled and cubic spline interpolated (signal processing Toolbox for MATLAB). From the single-lead ECG, we analyzed low-frequency power (LF: 0.04–0.15 Hz), high-frequency power (HF: 0.15–0.40 Hz), LF/HF ratio, LF% (the ratio between LF and the sum of LF and HF, expressed as a percentage), and HF% (the ratio between HF and the sum of LF and HF, expressed as a percentage).

Subjective symptoms were collected as a part of routine clinical intake forms (the Epworth Sleepiness Scale [ESS]) and postsleep exit forms administered to all patients undergoing testing (sleep quality score, with values 1–5, corresponding to the terms: poor, fair, average, good, and excellent), and perception of sleep latency (SL) duration and TST duration. For insomnia symptoms, the intake asks about the reason for testing (insomnia is an option), about quantifying sleep onset (we used >30 minutes), and number of awakenings (we used >3), subjective difficulty falling or staying asleep (we used binary "yes" answers). As we have done prior,[36–38] since we do not have more detailed clinical phenotyping of the insomnia diagnosis subtypes or severity, we used, as a correlate, the number of positive answers expressed by each individual. This intake form also allowed reporting of medications and comorbidities as check-boxes and free text, respectively. For medications, we performed a spelling correction script (modified in Python from http://norvig.com/spell-correct.html) and manual assignment to categories such as benzodiazepines, antihypertensives, new generation benzodiazepine receptor ligands (z-drugs), and hypnotics (which spanned other categories, such as benzodiazepines and z-drugs, but also included sedating antidepressants such as trazodone and mirtazepine). For each subject, the number of medications present in each category was given, allowing correlation approximations.

For measures of sleep perception, we used our recently described method of separating the latency and TST misperception.[39] In this way, misperception of TST is adjusted for sleep occurring during subjective SL to avoid double-counting among those with both onset and total sleep misperception.

The distribution of variables was mainly nonnormal, with only the amount of time in stage N2 (minutes) and the proportion of REM (%) meeting D'Agostino Pearson criteria for normality; for simplicity, we used therefore nonparametric (Mann–Whitney) methods for group-wise statistical testing and we used nonparametric Spearman correlation analysis to explore pair-wise relationships between variables. For comparing proportions, we used the Fisher exact test. Significance was defined by the P-value of <0.05, and due to the exploratory nature of our study, we did not correct for multiple comparisons.

Results

Clinical and PSG correlates of HR

HR changes during clinical PSG are heterogeneous. Figure 1 illustrates the following three clinical PSG examples: 1) a young adult male without OSA or PLMS that shows periods of relatively flat HR and periods of subtle increases in HR during sleep, 2) a middle aged female with PLMS and markedly elevated HR during sleep, and 3) an older female with severe OSA and prominent episodic HR elevations mirroring severe REM-related desaturations. A qualitative review of HR tracings in routine practice suggests that elevations can occur with or without concurrent pathology of movement or respiration and may occur in some portions of the night and not others. This prompted us to examine cardiac patterns in a large cohort from our sleep center database, consisting of n=1047 adults who underwent PSG for any indication; we excluded those with sleep apnea to remove this well-known cause of cardiac fluctuations. Table 1 reports the clinical features of the cohort, as well as some pertinent subsets.

We first sought to evaluate the distribution of HR dipping in the cohort. Figure 2A shows the mean HR values observed across stable bouts of sleep–wake stages, which were within ~2 bpm of each other. Small but statistically significant differences are noted for median HR in wake (62.3) vs REM (64.6), vs N1 (63.7), and vs N3 (64.2) but not vs N2 (62.9). To evaluate further these stage-wise comparisons, we next examined the distribution of HR dipping by comparing the mean HR during stable (>5 minutes long) wake bouts and the mean HR during stable NREM stages N2 and N3. Approximately 10% of subjects lacked a stable wake period, and thus the HR dipping analysis was performed on the remaining n=948 subjects. We found that only 13.5% exhibited at least 10% reduction of HR relative to wake; 31.2% show a reduction

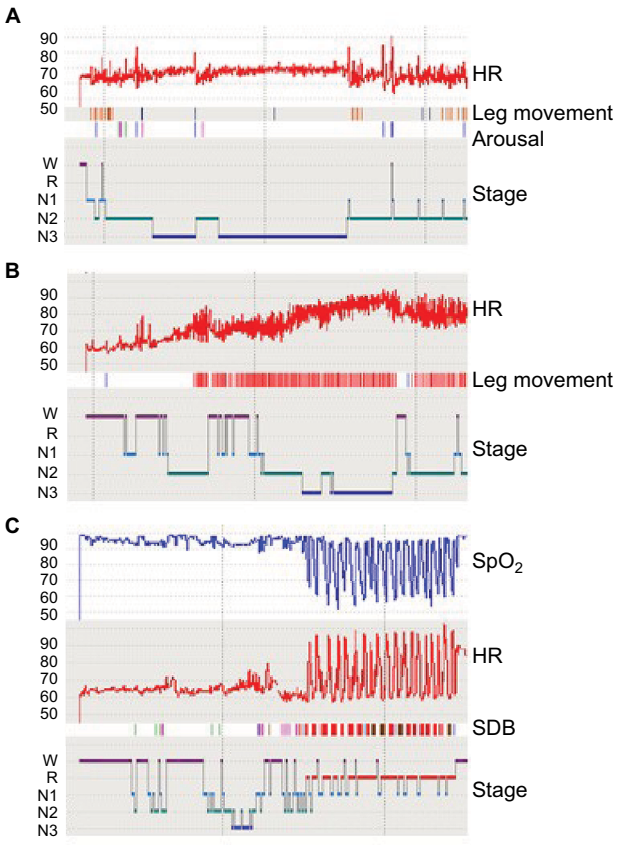


Figure 1 Examples of HR patterns from clinical PSGs.
Notes: (**A**) A 29-year-old male with fatigue, BMI 26 kg/m^2, with mildly increased HR trend in NREM sleep (all supine, absence of OSA, or PLMS). The top row shows HR values (bpm). The next row indicates scattered PLM events (limb movement). The third row indicates scattered AHI events. The bottom row shows the sleep–wake stages. In this and subsequent panels, the time scale is given as vertical dotted lines showing 1 hour intervals. In all panels, the recording time began between 10 and 10.30 pm. (**B**) A 51-year-old female with RLS and PLMS showing marked increase in NREM HR (all lateral position, BMI 25 kg/m^2, and absence of OSA). The top row shows HR values (bpm), the next row indicates PLMS events (limb movement), and the bottom row is sleep–wake stages. (**C**) An 80-year-old female with severe OSA (AHI 32), sleeping supine (BMI 30 kg/m^2), with reactive HR increases associated with REM desaturating events. The top row is the pulse oximetry data (SpO_2), the next row is the HR, the third row is the SDB events contributing to the AHI, and the bottom row shows the sleep–wake stages.
Abbreviations: AHI, apnea–hypopnea index; BMI, body mass index; HR, heart rate; NREM, nonrapid eye movement; OSA, obstructive sleep apnea; PLM, periodic limb movements; PLMS, periodic limb movements in sleep; PSG, polysomnography; REM, rapid eye movement; RLS, restless legs syndrome; SDB, sleep-disordered breathing.

of at least 5%, and 51.6% show any reduction (Figure 2B). Thus, nearly half of this cohort showed increased HR in stable N2 and N3 compared to wake.

We also analyzed HR reductions at the level of individual bouts, through an approximation based on the slope of the best fit line through the HR time series during stable bouts lasting at least 5 minutes (Figure S1). In other words, each stable bout of any stage was fitted this way and the resulting slopes (combined across all PSGs) were analyzed for their distribution. Figure 2C illustrates the cumulative distribution of slopes, according to sleep–wake stages. Wake contained the most variability, with relatively large proportions of both increasing and decreasing slope values represented. N3 showed the highest proportion of bouts showing a positive HR slope, of ~70%.

We next performed exploratory analysis to compare those with at least 10% HR dipping to the remainder of the cohort in terms of demographics, PSG metrics, and comorbidities. Using this cutoff, the group with at least 10% HR dipping was associated with younger age (33 vs 45; $P<0.001$), male sex (55% vs 37%; $P<0.001$), and lower body mass index (BMI) (25.7 vs 27.3 kg/m^2; $P<0.05$). To further explore sex differences, we analyzed a subset with no medications and no comorbidities (n=146; of whom n=81 males). Waking HR was lower in females than in males (55.8 vs 58.3; $P<0.0001$), while higher HR was observed in females for all sleep stages (N1: 64.9 vs 60.3, $P<0.05$; N2: 63.8 vs 58.1, $P<0.0001$; N3: 65.9 vs 58.5, $P<0.0001$; REM: 66.2 vs 60.9, $P<0.001$). Despite these higher HR values, the LH/HF ratio was lower in females (by 10%–20%) in all sleep stages ($P<0.05$). No sex differences were observed for age, BMI, ESS, TST, periodic limb movement index (PLMI), percent of any sleep–wake stage, or percent change in HR between wake and stable NREM. Of this group, n=124 could be assessed for HR dipping (some did not have stable wake bouts) and n=24 (20.2%) of these showed at least 10% HR dipping in stable NREM sleep, somewhat higher than seen in the full cohort. According to sex, n=9 of the 58 females (15.5%) and n=15 of the 66 males (22.7%) showed at least 10% HR dipping in stable NREM sleep. Any reduction in HR during stable NREM compared to stable was observed in 67.7% (n=84 of 124), again somewhat higher than observed in the full cohort, suggesting that medications, or comorbidities, or both, was contributing to some extent to the HR dipping physiology.

Small but statistically significant differences were noted in sleep architecture, with HR dipping being associated with lower N1% (5.9 vs 7.4; $P<0.05$), lower N2% (52.3 vs 53.4; $P<0.05$), higher N3% (19.5 vs 16.9; $P<0.05$), higher REM% (17.4 vs 15.7; $P<0.05$), and higher efficiency (86% vs 83%; $P<0.05$). TST and PLMI were not different according to dipping category. Misperception of TST was more prominent in those with HR dipping (32 minutes underestimation vs 14 minutes; $P<0.05$). HR dipping had significantly lower proportion of diabetes mellitus (1.6% vs 6.5%; $P<0.05$) and HTN (12.4% vs 21.0%; $P<0.05$) but did not differ in the proportion of anxiety, depression, heart failure, coronary disease, chronic obstructive pulmonary disease (COPD, stroke, insomnia symptoms, restless legs syndrome (RLS)

Table 1 Characteristics of the full cohort and clinically defined subsets

Metric	All	PLMI ≥15	ESS ≥11	MP ≥60 minutes
n	1047	339	285	283
Age (years)	43 (32–54)	49 (35–61)	41 (28–51)	40 (30–53)
Sex (% male)	39.5	45.4	33.3	32.5
BMI (kg/m^2)	27.3 (24.1–32.2)	27.2 (24.0–32.2)	26.8 (23.7–31.7)	27.2 (24.0–32.3)
ESS	7 (4–12)	7 (3–11)	13 (12–16)	6 (3–11)
TST (minutes)	384 (339–423)	368 (311–409)	400 (366–429)	395 (352–430)
N1%	10.6 (6.6–16.3)	14.6 (9.2–21.2)	9.7 (5.5–15.0)	10.9 (6.7–16.3)
N2%	53.6 (46.6–60.8)	53.6 (46.0–61.4)	53.7 (46.8–60.7)	52.9 (45.2–60.3)
N3%	17.4 (10.7–23.3)	14.4 (7.6–21.7)	17.7 (10.9–22.7)	18.8 (11.0–24.0)
REM%	16.0 (11.0–21.3)	14.7 (8.4–19.5)	16.7 (12.2–21.7)	16.0 (11.1–21.3)
Efficiency (%)	85 (76–91)	80 (69–88)	88 (81–93)	86 (78–91)
SL (minutes)	6.0 (2.0–14.0)	6.5 (2.5–16.5)	5.5 (2.0–12.8)	6.5 (2.5–13.0)
PLMI (1/hour)	7.4 (2.4–20.8)	31.6 (21.3–56.4)	6.8 (2.0–15.4)	6.7 (2.4–17.4)
HR–wake	62.3 (54.5–70.6)	61.5 (54.9–70.5)	62.6 (54.8–72.1)	63.9 (55.6–71.2)
HR–N1	63.7 (57.2–71.4)	63.4 (56.8–71.1)	65.5 (59.1–72.5)	64.8 (58.8–72.2)
HR–N2	62.9 (56.0–69.3)	62.5 (55.6–68.7)	63.5 (56.6–70.6)	63.5 (56.4–69.2)
HR–N3	64.2 (57.2–71.4)	63.5 (55.8–70.6)	64.8 (58.3–72.3)	64.8 (58.4–71.5)
HR–REM	64.6 (57.8–71.4)	63.2 (56.5–70.2)	65.5 (59.1–71.7)	65.6 (58.4–71.8)
Depression (%)	36.0	37.5	42.5	37.1
Anxiety (%)	41.5	41.3	44.2	43.8
Hypertension (%)	19.5	22.7	19.0	17.1
COPD (%)	1.5	1.8	1.8	1.4
CAD (%)	1.8	3.0	1.8	1.1
CHF (%)	1.5	1.5	1.8	1.1
DM (%)	6.1	6.8	6.0	6.7
Stroke (%)	2.1	4.4	2.5	1.4

Note: Data are either median (IQR) or percentage as noted.

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESS, Epworth Sleepiness Scale; HR, heart rate; HRV, HR variability; IQR, interquartile range; MP, misperception; PLMI, periodic limb movement index; REM, rapid eye movement; SL, sleep latency; TST, total sleep time.

symptoms, ESS, or sleep quality. Certain medications were less frequently reported in those with HR dipping, such as opiates, antidepressants, benzodiazepines, anti-HTN, and hypnotics (but not z-drugs in particular), while there were no differences in antihistamine, antidiabetic, or stimulant medications.

Clinical and PSG correlates of spectral cardiac metrics

We next explored frequency measures of HRV, derived from stable bouts (>5 minutes) of each sleep–wake stage, for potential relationships to subjective sleep measures: sleepiness via the ESS; a 5-point sleep quality scale referring to the specific night of the PSG; and the degree of misperception of TST referring to the specific night of the PSG ("Methods" section). Table 2 shows all correlation values >0.10 (or <–0.1) between HF, LF, or their ratio for either the ESS or the sleep quality metric. Misperception was positively correlated with the LF value in N1, and LF/HF ratio in N1, and negatively correlated with the HF% in stage N1. In addition, we examined potential relationship of HRV frequency metrics with an objective form of sleep disturbance, the PLMI. The PLMI was positively correlated with the N1 and N2 LF/HF ratio and negatively correlated with the percentage of HF in stable N1 and N2.

Figure 3A and B shows the distribution of two strongly associated clinical factors, age, and N1%, across categories of PLMI values. Figure 3C shows the significant correlates for PLMI, spanning clinical, sleep staging, and cardiac metrics. Of the 18 significant factors, 10 factors were related to cardiac function and suggested that PLMI correlated with altered autonomic balance: increased LF power and LF/HF ratio and decreased HF power. There was no relation to antidepressant medication use, or insomnia symptoms, or was there any relation to the ESS value or the sleep quality value.

Figure 4 summarizes correlates of sleep quality and sleep misperception. Sleep quality showed fewer correlates than PLMI values, most notably a positive correlation with sleep efficiency (Figure 4A) and with TST misperception (Figure 4B). Correlations reaching the prespecified level of at least |0.1| are given in Figure 4C for sleep quality, and Figure 4D for TST misperception values. No HRV values

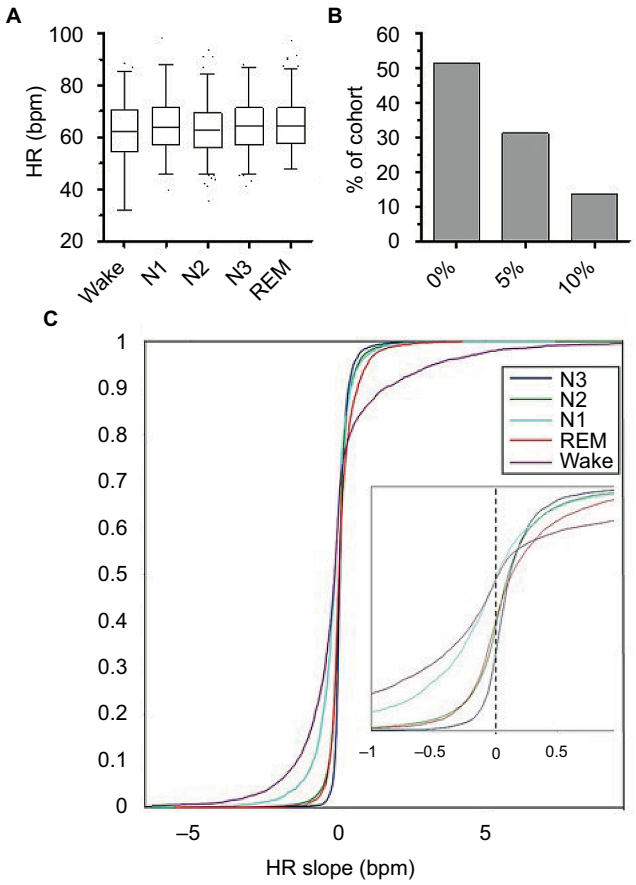


Figure 2 HR analysis across sleep–wake stages.
Notes: (**A**) HR values calculated from stable bouts (>5 minutes) of each sleep–wake stage. There were no differences between any of the stages. The waking HR values refer to any time spent awake while in bed for the PSG recording. (**B**) Histogram showing the proportion (%) of the cohort with lower HR value during N2 and N3, compared to wake of at least 0, 5, or 10% dipping. (**C**) Distribution of HR slope calculated for stable bouts of each sleep–wake stage across the cohort. The *X*-axis is the slope of a linear fit to each stable bout (in units of bpm). The zero-crossing value is the proportion of stable bouts that had a positive slope, and the inset is a zoom to show that the highest value was for wake and N1; by contrast, N3 had the greatest proportion of bouts showing a positive slope (lowest zero-crossing value on the *Y*-axis).
Abbreviations: HR, heart rate; PSG, polysomnography; REM, rapid eye movement.

Table 2 HRV correlations with selected clinical features

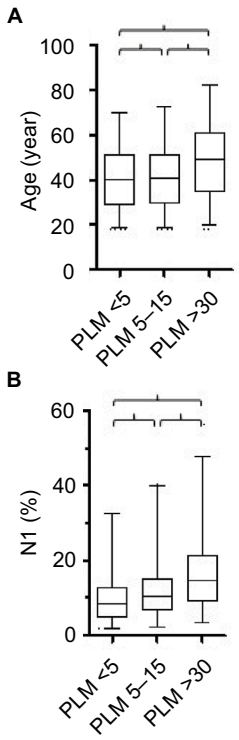
Metric	ESS	Quality	TST MP	PLMI
N1 LF	0.07	–0.03	**0.14****	0.07
N1 HF	0.06	–0.05	–0.01	–0.04
N1 HF%	0.01	–0.03	**–0.13****	**–0.13****
N1 ratio	–0.01	0.06	**0.14****	**0.16****
N2 LF	–0.02	–0.04	0.01	0.06
N2 HF	–0.01	0.02	–0.02	–0.03
N2 HF%	0.00	0.07	–0.03	**–0.10***
N2 ratio	–0.01	–0.05	0.03	**0.11****
N3 LF	0.01	–0.04	0.02	–0.03
N3 HF	0.05	0.00	0.04	**–0.13****
N3 HF%	0.04	0.04	0.02	**–0.12****
N3 ratio	–0.03	–0.03	–0.02	**0.14*****
REM LF	0.02	0.02	0.00	–0.05
REM HF	0.04	0.07	–0.01	–0.01
REM HF%	0.05	0.08	-0.03	0.00
REM ratio	–0.06	–0.05	0.03	0.02
W LF	0.05	–0.03	0.06	0.06
W HF	0.06	0.02	0.04	0.01
W HF%	0.05	0.02	–0.01	–0.05
W ratio	–0.05	0.01	0.01	0.06

Notes: *R*-values are bold if >0.10 (Spearman correlation coefficient). *P<0.05, **P<0.005, and ***P<0.0005.
Abbreviations: ESS, Epworth Sleepiness Scale; HF, high frequency; HRV, heart rate variability; LF, low frequency; MP, misperception; PLMI, periodic limb movement index; REM, rapid eye movement; TST, total sleep time; W, wake.

were related to sleep quality, but HR dipping was associated with higher quality, as was lower HR in wake. Misperception of TST was only related to HRV metrics from stage N1, which is the lowest prevalence stage in most of the PSGs. Moreover, the relationship would appear the opposite as expected: increased LF power and LF/HF ratio were correlated with less misperception. However, we previously reported a similarly unexpected finding that misperception was associated with more stable sleep (fewer transitions) based on standard stage scoring.[39]

The ESS score was inversely correlated with age (R=–0.12) insomnia (R=–0.15), and positively correlated with TST (R=0.22) and sleep efficiency (R=0.21; itself correlated with TST) (data not shown).

Finally, we explored the combination of objective TST and insomnia symptoms to parallel the work of Vgontzas et al,[40] who suggested that insomnia with objective short TST on PSG testing is the most severe sub-phenotype from a medical and psychiatric risk standpoint. We prespecified categories as follows: objective TST cutoff 5.5 hours, taking a mid-pint between the cutoff values of either 5 or 6 hours used by Vgontzas et al, and the degree of insomnia symptoms as either high or low ("Methods" section). Table 3 shows different clinical and PSG-derived features that differed significantly between those with >5.5 hours of TST and low insomnia symptoms vs those with <5.5 hours of TST and high insomnia symptoms. Figure 5 focuses on key metrics and includes the two other possible combinations (>5.5 hours TST and high insomnia symptoms and <5.5 hours TST and low insomnia symptoms). Short TST was associated with younger age, regardless of insomnia symptom category. Similarly, short TST was associated with higher N1%, lower REM%, lower sleep efficiency, and higher PLMI, in each case independent of insomnia symptom category. HR values across the five sleep–wake stages showed more subtle and variable differences. For example, wake HR was significantly higher in the short TST with high insomnia group, compared to the long TST with low insomnia group. HR was higher in the high insomnia group for N2 and N3 and REM stage,



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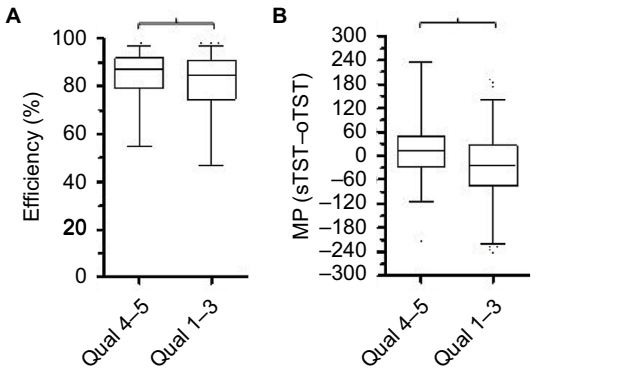
Factor	*R*-value
N1%	0.36
Age	0.22
N1 ratio	0.14
N1 LF%	0.13
N3 ratio	0.12
N3 LF%	0.12
anti-HTN	0.12
WHR slope	0.11
N2 ratio	0.11
N2 LP%	0.11
TST MP	0.10
N2 HF%	–0.11
N3 HF%	–0.12
N1 HF%	–0.13
N3%	–0.18
REM%	–0.19
TST	–0.21
Efficiency	–0.26

Figure 3 Clinical, PSG, and cardiac correlates of PLMS.
Notes: (**A**) Box and whiskers plot showing the distribution of age (years) for three prespecified categories of PLMI values. Brackets indicate significant differences between groups (Kruskal–Wallis with Dunn's correction, $P<0.0001$). (**B**) Box and whiskers plot showing the distribution of N1 (%) for three prespecified categories of PLMI values. Brackets indicate significant differences between groups (Kruskal–Wallis with Dunn's correction, $P<0.0001$). (**C**) Correlation coefficients reaching the predefined minimum value of $|>0.1|$, with the PLMI value across the cohort. *P*-values were $<1\times10^{-8}$ for N1%, age, N3%, REM%, TST, and efficiency. The remaining significant *p*-values were between 0.01 and 0.0001.
Abbreviations: HF, high frequency; HR, heart rate; HTN, hypertension; LF, low frequency; MP, misperception; PLM, periodic limb movements; PLMS, periodic limb movements in sleep; PLMI, periodic limb movement index; PSG, polysomnography; REM, rapid eye movement; TST, total sleep time; WHR, wake heart rate.



C
Quality correlates

Factor	*R*-value
Efficiency	0.19
MP	0.17
TST	0.14
Neuroleptic	0.10
% HR dip	–0.11
HR wake	–0.13
N1%	–0.15

D
Misperception correlates

Factor	*R*-value
Quality	0.17
N1 LF/HF ratio	0.14
N1 LF power	0.14
N1 LF%	0.13
z-drug	0.11
TST	–0.12
N1 HF%	–0.13

Figure 4 Clinical, PSG, and cardiac correlates of sleep quality and of misperception.
Notes: (**A**) Box and whiskers plot showing the distribution of sleep efficiency (%) for prespecified categories of sleep quality. Bracket indicates significance (Mann–Whitney, $P<0.003$). (**B**) Box and whiskers plot showing the distribution of misperception of TST (subjective minus objective TST, in minutes) for prespecified categories of sleep quality. Bracket indicates significance (Mann–Whitney, $P<0.0001$). (**C**) Correlation coefficients reaching the predefined minimum value of $|>0.1|$, with the sleep quality value across the cohort. The *P*-values are all <0.005. (**D**) Correlation coefficients reaching the predefined minimum value of $|>0.1|$, with the TST misperception value across the cohort. The *P*-values are all <0.005.
Abbreviations: HF, high frequency; HR, heart rate; LF, low frequency; MP, misperception; oTST, objective TST; PSG, polysomnography; Qual, quality; sTST, subjective TST; TST, total sleep time; z-drug, zolpidem, zaleplon, eszopiclone.

compared to the low insomnia group, largely independent of TST grouping. In summary, age and PSG metrics were more strongly associated with short TST, while HR changes across stages seemed to track insomnia symptom category more strongly than the TST category. Additional exploratory correlations are given in Figure S2 separately for objective TST and for insomnia symptoms.

Discussion

Clinical sleep medicine faces competing pressures when pursuing objective evaluations of sleep physiology. On one hand, the allure of personalized medicine based on careful phenotyping is making rapid gains in terms of sleep apnea,[41–44] insomnia,[40,45] PLMS,[22] autonomic dysfunction,[46] cardiovascular physiology,[1] and sleep fragmentation.[47,48] On the other hand, resource shifts toward at-home diagnostics, with limited-channel devices designed for uncomplicated OSA detection,[49] are unlikely to directly support improved phenotyping efforts. Efforts to improve in-laboratory PSG-based phenotyping[43,50,51] could improve risk stratification and guide care decisions. The information contained in cardiac channels is well suited for implementation via both in-laboratory and at-home diagnostics, as cardiac physiology (either HR or ECG) is present in both clinical recording contexts. The current work describes a large and heterogeneous cohort without sleep apnea, in which the wide range of cardiac physiology illustrates both the challenges and the potential for clinically relevant phenotyping in a practice setting. For example, important patterns such as HR nondipping, and frequency metrics of HRV for autonomic balance, were only weakly correlated at the population level with clinical predictors. This implies that without objective testing, these physiological phenotypes may go largely unrecognized. Given that pathological signatures in the cardiac signals, both routine (HR) and advanced (HRV), are common even in those without OSA,

Table 3 Objective short TST with insomnia symptoms

Metric	>5.5 hours TST	<5.5 hours TST
Age (years)	**41 (29–52)*****	**49 (41–61)**
Male (%)	41.7	44.0
BMI (kg/m^2)	27.3 (24.0–31.8)	27.0 (23.8–31.9)
ESS	9 (5–13)***	5 (3–8)
TST (minutes)	403 (374–429)***	292 (257–313)
N1%	9.7 (5.8–14.6)***	15.7 (9.0–25.0)
N2%	53.0 (46.2–60.1)	53.3 (44.0–62.3)
N3%	18.0 (12.0–23.0)	16.4 (6.1–25.4)
REM%	**17.6 (12.8–21.9)*****	**9.8 (4.6–16.8)**
Efficiency (%)	**89 (82–93)*****	**65 (56–73)**
SL (minutes)	**4.5 (1.5–11.5)*****	**10.5 (4.5–32.3)**
PLMI (1/hour)	**6.5 (2.0–17.0)*****	**13.9 (4.5–34.1)**
HR–wake	**61.0****	**64.9**
HR–N1	**62.3****	**64.6**
HR–N2	**61.7****	**64.9**
HR–N3	**64.0***	**67.4**
HR–REM	**63.3***	**67.8**
Depression (%)	32.6	39.5
Anxiety (%)	35.8	45.0
HTN (%)	**16.6***	**27.5**
COPD (%)	1.4	0.9
CAD (%)	**1.0****	**6.4**
CHF (%)	**0.6***	**3.7**
DM (%)	4.9	9.2
Stroke (%)	1.4	3.7
N1 LF	6.3 (5.1–7.4)	6.3 (5.0–7.7)
N1 HF	5.7 (4.4–7.0)	5.5 (3.9–7.1)
N1 HF%	47.6 (41.7–55.1)	45.8 (40.3–52.2)
N1 ratio	1.1 (0.8–1.4)	1.2 (0.9–1.5)
N2 LF	8.5 (7.4–9.9)	8.7 (7.2–10.0)
N2 HF	7.6 (6.2–9.1)	7.5 (6.3–9.2)
N2 HF%	46.7 (41.0–52.2)	45.3 (40.1–51.6)
N2 ratio	1.2 (0.9–1.5)	1.3 (1.0–1.6)
N3 LF	8.7 (7.2–10.6)	8.7 (6.8–10.9)
N3 HF	9.1 (7.0–11.6)	9.6 (6.6–12.4)
N3 HF%	51.0 (45.4–56.2)	48.4 (44.7–58.3)
N3 ratio	1.0 (0.8–1.3)	1.1 (0.7–1.3)
REM LF	8.0 (6.5–9.6)	7.2 (5.8–9.0)
REM HF	6.3 (4.7–8.0)	5.4 (3.8–7.0)
REM HF%	43.4 (38.3–48.4)	42.6 (35.7–49.5)
REM ratio	1.3 (1.1–1.7)	1.4 (1.0–1.8)
W LF	5.9 (4.6–7.8)	6.8 (5.2–8.3)
W HF	5.5 (3.8–8.2)	6.5 (4.4–9.1)
W HF%	47.5 (41.3–52.6)	46.0 (42.9–51.7)
W ratio	1.2 (0.9–1.5)	1.3 (1.0–1.5)

Notes: Data are median (IQR) or percentage. Bold indicates significance: *P<0.05, **P<0.001, and ***P<0.0001.

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESS, Epworth Sleepiness Scale; HF, high frequency; HR, heart rate; HTN, hypertension; LF, low frequency; PLMI, periodic limb movement index; REM, rapid eye movement; SL, sleep latency; TST, total sleep time; W, wake.

further work is needed to explore mechanistic hypotheses and to bring cardiac phenotyping into a clinical practice that largely overlooks this information in sleep diagnostics. Exploring large datasets, either from clinical sources as we performed or from research registries (such as www.sleepdata.org), can support phenotyping hypothesis testing in sub-groups by age, sex, medications, comorbidities, and if longitudinal follow-up is captured, in clinical outcomes.

HR dipping and HRV correlates in the current study

In this cohort, nearly half of the subjects showed an increase in HR during stable N2 and N3 compared to wake. Younger age and male sex were most strongly correlated with HR dipping. Diabetes and HTN were the comorbidities linked to nondipping HR. Interestingly, the PLMS values were not related to HR dipping, which ran counter to our prediction that elevated PLMS would cause more consistent HR elevations.[22,23,52,53] Further analysis of event-linked HR transients may shed light on whether individual heterogeneity blurred correlations at the group level. Medications and/or comorbidities may explain some of the HR nondipping patterns, as a subset with no medications or comorbidities showed more common HR dipping.

We found no relationship between the ESS value and HR or HRV measurements; previous studies in other populations also found little relation.[54,55] Sleep quality scores, referring to the night of PSG specifically, showed only very small correlations, being inversely related to the mean HR in wake (R=–0.13) and the percentage HR dipping (R=–0.12). The former relation is plausible, if perhaps higher HR during wake reflects a form of hyperarousal that influences the perception of sleep quality. Interestingly, although these correlations were small, they were of a similar magnitude of quality correlations with other metrics such as TST (0.14), sleep efficiency (0.19), and N1% (–0.15). Whether pharmacological or behavioral measures designed to reduce nocturnal HR can improve sleep quality remains an interesting possibility.[56,57]

Physiological correlates of insomnia and misperception

Although the clinical diagnosis and management of insomnia do not routinely involve objective sleep measurements, extensive work describes the physiology-based subphenotypes of insomnia[17,58,59] beyond the typical diagnostic heuristics. HRV analysis has shown increased LF and reduced HF power during sleep,[60,61,16] consistent with an autonomic facet of the increased arousal model.[17] There

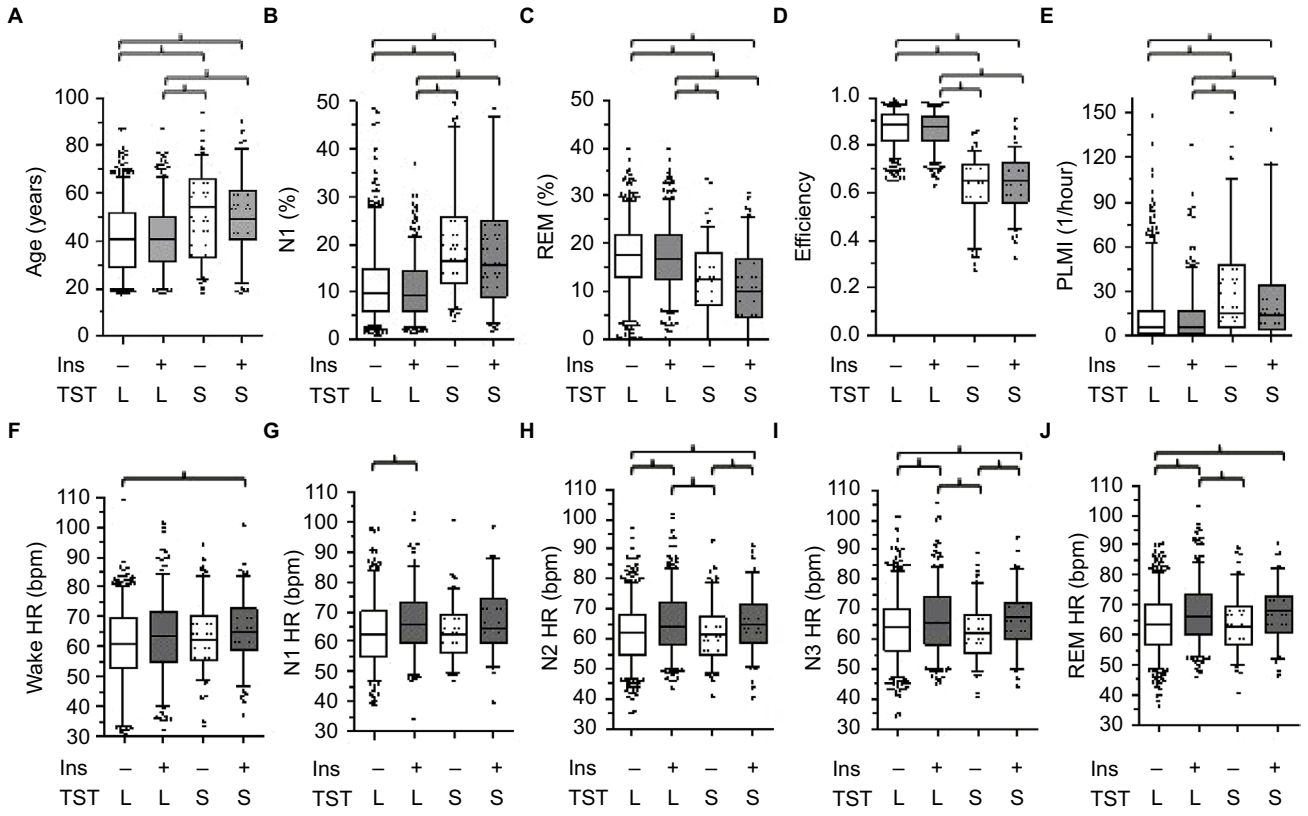


Figure 5 Insomnia symptoms and objective TST.

Notes: The four possible combinations of binary total sleep time (TST; long [L] or short [S]) and insomnia symptom status (+ or –) are shown for age (**A**), N1 % (**B**), REM % (**C**), efficiency (**D**), PLMI (**E**), wake HR (**F**), N1 HR (**G**), N2 HR (**H**), N3 HR (**I**), and REM HR (**J**). In each panel, the box and whisker plots (5%–95%, with outliers shown as dots to illustrate variability) are given for four sub-cohorts based on objective TST value from the PSG (5.5 hours cutoff, for L or S values, and insomnia symptom level (high as + sign, low as - sign). These categories are given via *X*-axis labels, as well as the fill of the box plots: gray indicates insomnia symptom +, and speckled indicates <5.5 hours TST. Kruskal–Wallis testing results are shown with Dunn's post hoc comparison of all possible group-wise pairs in each panel, where brackets indicate significant differences. The *P*-values were <0.0001 for all panels except wake and N1% ($P<0.005$).

Abbreviations: HR, heart rate; Ins, insomnia; L, long; PLMI, periodic limb movements index; PSG, polysomnography; REM, rapid eye movement; S, short; TST, total sleep time

is some suggestion that the HRV frequency abnormalities are mainly present in those insomnia patients with short objective sleep duration.[62] Importantly, work by Vgontzas et al demonstrated the importance of objective sleep duration (defined during PSG), over that of subjective reporting of insomnia, for incident medical and psychiatric morbidities.[40,45]

Despite extensive work investigating the basis of misperception, the causes remain the subject of discussion.[36,39,63] We found that misperception of TST was associated with HR dipping, which runs counter to the prediction that dipping should reflect better sleep quality. TST misperception was only related to HRV frequency metrics derived from stage N1 and, in a manner that suggests more stable cardiac function, was related to greater misperception, which does not support the hypothesis that sympathetic tone contributes to the under-estimation of sleep. These somewhat unexpected relationships could be epi-phenomena: if more stable sleep is associated with longer TST, this would allow more opportunity to underestimate.[39]

Clinical and physiological correlates of PLMS

PLMS is most commonly associated with clinical RLS, but this relationship is asymmetric: most individuals with elevated PLMI values do not have RLS.[64] PLMS has been associated with a variety of neuropsychiatric[65–76] and systemic disorders, in addition to reports among sleep disorders such as insomnia,[77,78] sleep apnea,[71,79] and narcolepsy.[74] Although much exciting work continues to evolve in regard to the physiology and clinical correlates of PLMS,[80,81] perhaps the most important consideration is the association between PLMS and cardiovascular and cerebrovascular outcomes.[82–84] This association may be mechanistically related to sympathetic arousal[85] and with both nocturnal and daytime HTN.[86,87] HRV analysis of adults with PLMS suggests increased LF values and the LF/HF ratio associated with events,[53,88] and similar findings were reported in children.[89]

As we reported previously in a smaller cohort, the clinical prediction of elevated PLMS is challenging, with only modest correlations arising from demographic and clinical history information.[79] In the current cohort, PLMI was most strongly predicted by advancing age and use of antihypertensives. Sixteen of the other 18 correlated factors were PSG-derived metrics, most of which were cardiac physiology. No relation was found with antidepressant medications.[90] A recent systematic review suggested that the increased PLMS values with certain antidepressants were unlikely to be of clinical importance given the lack of disruption of sleep;[91] however, as noted earlier, autonomic "disturbance" is possible even when EEG changes are minimal.

Cardiovascular measures in sleep disorders and cardiovascular risk

Frequency measures of HRV reveal that normal NREM sleep, especially slow wave (N3), is associated with increased HF power and reduced LF power (and lower LF/HF ratio), while the opposite pattern is observed in REM sleep.[92–97] Blood pressure and HR reduction are also evident in stable NREM sleep.[98] Alterations in these normal patterns, especially blunting of the NREM stability pattern, may occur with a variety of sleep disorders and have been associated with cardiovascular morbidity and mortality.[2] OSA is associated with well-described alterations in HRV, with increased LF, reduced HF, and increased LF/HF ratio consistent with the sympathetic overdrive mechanisms of this disorder.[99–103]

Ben-Dov et al[24] reported increased all-cause mortality with HR nondipping in sleep in a large cohort who underwent ambulatory blood pressure monitoring, a somewhat larger effect than for nondipping of blood pressure. In that cohort, HR nondipping was associated with increased age and BMI, female sex, and comorbidities of HTN and diabetes (treated). In another ambulatory blood pressure monitoring cohort, Eguchi et al[104] reported nocturnal HR nondipping to be associated with cardiovascular events, but not all-cause mortality. In that cohort, HR nondipping was unrelated to age, sex, BMI, diabetes, or antihypertensive medications. In yet another cohort, cardiovascular risk was increased in those with nocturnal nondipping of both blood pressure and HR.[105]

These prior studies used daytime measures to define the awake HR, which may result in higher HR values than those obtained during wake from our current study; the awake time was in a recumbent position throughout nocturnal PSG testing. Only about half of the subjects in our cohort showed HR dipping of any degree in sleep compared to wake. Further studies using 24-hour cardiac monitoring, including PSG to identify sleep stages, would better characterize the phenotype of HR dipping relative to daytime-wake physiology. Sleep staging is critical for intermittent cuff studies, as REM sleep and transitional sleep are associated with HR fluctuations, which could add noise to intermittent cuff inflation approaches (every 30 or 60 minutes measurement).

Limitations

This study has several limitations, some of which are addressable in future analysis or prospective study designs. This was a cross-sectional cohort, with only one night of PSG. While this is reflective of current practice standards, night-to-night variability may play in important role in sleep phenotyping. We do not have information regarding circadian rhythm or light exposure of patients coming into the sleep laboratory, each of which could impact cardiac physiology. The medications and comorbidities were self-reported and we do not have corroborating data from the electronic medical record about compliance or dosing, or the duration or severity of comorbidities. Together, these uncertainties contribute noise to our measurements and blur potential associations, which suggest that the strength of the relationships we did identify might be underestimated. In the future, with even larger cohorts, sub-categorizing the data by age, sex, comorbidities, and medications may still allow sufficient sample sizes remaining in each group to support physiological analysis. Most importantly, we do not have outcome information for clinical course, adverse events, or treatment response for these subjects. Future studies of outcomes could be undertaken by matching records of such retrospective cohorts with increasingly available electronic medical information in large hospital systems such as ours.

Disclosure

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Supplementary materials

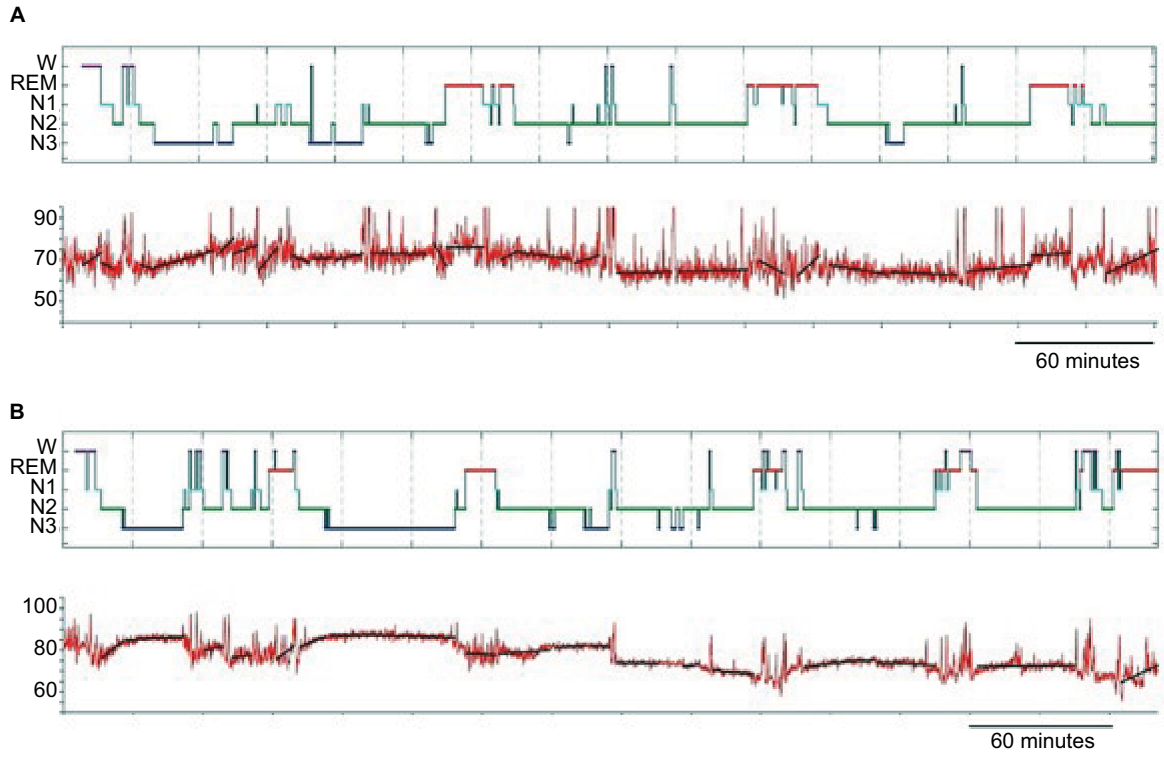

Figure S1 Examples of HR slope assessments from clinical PSGs.
Notes: In (**A**) and (**B**), the scored hypnogram is shown above the HR tracing derived from the pulse oximetry signal as visualized through the Grass software. The HR units (*Y*-axis) are in beats per minute. The color scheme of the stages is the same as in Figure 1 of the main text. Stages are indicated on the *Y*-axis. Time base is given for an 1 hour increment (and hash marks on the *X*-axis are 30 minutes apart). For each sleep–wake stage bout of 35 minutes ("stable" bouts), the calculated best fit line is super-imposed on the HR trace (black lines).
Abbreviations: HR, heart rate; PSGs, polysomnography; REM, rapid eye movement; W, wake.

A TST correlates

Factor	*R*-value
Efficiency	0.87
REM %	0.34
ESS	0.22
Sleep Qual	0.14
REM LF power	0.10
Wake HR	–0.11
TST MP	–0.12
Sex	–0.13
CHF	–0.14
Wake HF power	–0.14
HTN	–0.16
anti-HTN drug	–0.19
Wake LF power	–0.19
PLMI	–0.27
Age	–0.28
N1%	–0.41

B Insomnia correlates

Factor	*R*-value
RLS symptoms	0.21
Any hypnotic	0.20
z-drug	0.19
Anxiety	0.18
RLS/PLMS drug	0.17
Depression	0.15
N2 HR	0.15
REM HR	0.15
Any neuroactive	0.15
N3 HR	0.14
Any herbal hyp	0.13
Sex	–0.11
ESS	–0.15

Figure S2 Correlations with TST and with insomnia symptoms.
Notes: (**A**) Significant correlations above the prespecified minimum of >|0.1| for the PSG-derived TST value. (**B**) Significant correlations above the prespecified minimum of >|0.1| for insomnia symptoms ("Methods" section).
Abbreviations: CHF, congestive heart failure; ESS, Epworth Sleepiness Scale; HF, high frequency; HR, heart rate; HRV, HR variability; HTN, hypertension; hyp, hypnotic; LF, low frequency; MP, misperception; PLMI, periodic limb movement index; PLMS, periodic limb movements in sleep; PSG, polysomnography; Qual, quality; REM, rapid eye movement; RLS, restless legs syndrome; TST, total sleep time; z-drug, zolpidem, zaleplon, eszopiclone.