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RESEARCH ARTICLE

Nighttime cardiac sympathetic hyper-activation in young primary insomniacs

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Abstract
Purpose A growing literature supports the association between insomnia and cardiovascular risk. Since only few studies have provided empirical evidence of hyper-activation of the cardiovascular system in insomniacs, the aim of the present study was to analyze cardiac autonomic responses in primary insomnia.
Methods Impedance cardiography and heart rate variability (HRV) measures were assessed in 9 insomniacs and 9 good sleepers during a night of polysomnographic recording.
Results Insomniacs were found to be characterized by a constant sympathetic hyper-activation which was maintained all night, as suggested by a faster pre-ejection period (PEP) compared to good sleepers. In addition, only insomniacs showed a strong reduction in heart rate in the transition from wake to sleep. Both groups exhibited a reduction in cardiac output and sympathovagal balance, i.e., reductions in low-frequency/high-frequency ratio and increases in high-frequency normalized units of HRV, across the night. In addition, in our sample, a high physiological sympathetic activation (fast PEP) at night was found to be directly associated with low quality of sleep.
Conclusions These preliminary findings suggest that a constant cardiac sympathetic hyper-activation throughout the night is a main feature of primary insomnia. Our evidences support the association between insomnia and increased risk for cardiovascular diseases.

Keywords Insomnia · Hyper-arousal · Cardiovascular activity · Autonomic functioning · Heart rate variability

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Introduction

Primary insomnia is defined as difficulty initiating or maintaining sleep, or non-restorative sleep, for at least 1 month that results in clinically significant distress or impairment in social, occupational, or other important areas of functioning. Furthermore, the sleep disturbance does not occur as a consequence of another sleep or psychiatric disorder and is not due to substance use or a general medical condition [1].

In addition to nocturnal symptoms, daytime consequences are frequently reported by insomniacs (e.g., daytime sleepiness, fatigue, mood disturbances). Moreover, cognitive dysfunctions seem to be present in insomnia [12, 15]. Insomnia is also frequently associated with depression and anxiety [32].

Growing literature is focused on the association between insomnia and cardiovascular risk [21, 22, 30]. Several studies have provided evidence that elevated blood pressure [37], resting heart rate [11, 16], sympathetic hyper-activity [17] and autonomic imbalance [33] play a key role in increasing the cardiovascular risk. Whereas a generalized condition of hyper-arousal has been thought to underlie the primary insomnia condition [4], evidence of hyper-activation of the cardiovascular system in this disorder is still sparse.

Several studies suggest that insomniacs compared to good sleepers are characterized by elevated heart rate [3, 18, 31] and blood pressure [21]. Differently, other studies failed to provide group differences over these variables [14, 19, 29, 36]. Autonomic activity has been non-invasively investigated in primary insomnia by means of heart rate variability (HRV) analysis. Spectral analysis of inter-beat intervals (IBIs) provides indexes of both sympathetic and vagal cardiac activity. Activity that occurs between 0.04 and 0.15 Hz is considered reflecting a relatively sympathetic dominance, while activity in the range of 0.15–0.4 Hz reflects vagal predominance [10]. Notwithstanding that primary insomnia has been thought to be associated with increased low-frequency power [3] and decreased high-frequency power [3, 29] during the night, indicating higher sympathetic and lower parasympathetic activation, respectively, other studies provided contrasting results [14, 19, 36]. In addition, the pre-ejection period (PEP), an index inversely related to the cardiac beta-adrenergic sympathetic autonomic activity, was found to be significantly faster at sleep onset in insomniacs [13], suggesting a sympathetic hyper-activation during the falling asleep process. On the other hand, PEP was found to be not statistically different between insomniacs and good sleepers in a constant routine study [36].

Since only few studies have been focused on the nocturnal cardiovascular activity in insomnia population providing elusive results, our purpose was to investigate nocturnal cardiovascular modifications in primary insomniacs compared with good sleepers, focusing on cardiac autonomic functioning. For this purpose, we adopted HRV analysis and impedance cardiography technique. Based on our previous results [13], we aimed at determining whether the sympathetic nervous system hyper-activation found at sleep onset in insomniacs is maintained throughout the night, as well as if it is linked to the perceived arousal and the quality of sleep.

Methods

Participants

The study involved 18 undergraduates, 9 insomniacs (4 men and 5 women; mean ± SD age: 23.00 ± 2.40 years; range 20–26 years) and 9 good sleepers (4 men and 5 women; mean ± SD age: 23.56 ± 3.17 years; range 19–28 years). Participants were recruited through advertisements posted at the faculties of the University of Padova.

Insomniacs were enrolled according to the DSM-IV [1] diagnostic criteria for primary insomnia. Participants were also administered a semi-structured clinical interview to collect anamnesis and investigate sleep history, and medical and psychological state. Insomniacs had also to report a history of insomnia for at least 1 year. Additional exclusion criteria were body mass index (BMI; kg m^{-2}) $\geq$30, use of psychoactive medication or drugs, medical and/or psychiatric conditions and shift work or time-zone travel in the 6 months prior to the study. Actigraphy data and sleep logs were collected for 1 week prior to the nighttime study to exclude circadian disorders.

All participants were informed about the purpose of the research and they gave written informed consent; they also received a compensation of 100 Euros. The study protocol was approved by the Ethic Committee of the Department of Psychology and was in accordance with the Helsinki Declaration.

Experimental protocol

Polysomnographic recordings were collected over two consecutive nights with an adaptation night preceding the experimental night. Only data recorded during the second night were analyzed. On each night, subjects arrived in the laboratory at 8:00 p.m. and the equipment was attached. Participants were put to bed 15 min before midnight, while the lights were turned off at midnight. Subjects were requested to go to sleep and they were left undisturbed until wake-up time at 8:00 a.m. Physiological data were analyzed from midnight to 8:00 a.m. as a function of sleep stage (wake, stage 1, stage 2, SWS and REM sleep).

Participants refrained from consuming tobacco, alcohol and caffeine during the 24 h preceding each night. The experiment was conducted in a quiet, soundproof, comfortable room in the Psychophysiology Sleep Laboratory, Department of General Psychology, University of Padova.

Dependent variables

Subjective measures

Subjective quality of sleep was assessed by the Pittsburgh Sleep Quality Index [PSQI; 9] and by the Athens Insomnia Scale [AIS; 28]. In addition, perceived level of arousal was assessed by the Hyperarousal Scale [HS; 25].

Polysomnographic recordings

Polysomnography was performed using four electroencephalographic (EEG) leads (C_3-A_2, C_4-A_1, F_3-A_2, F_4-A_1), monocular electrooculograms (EOG) and bipolar submental electromyogram (EMG). Signals were acquired on a BIOPAC MP100 acquisition system (BIOPAC Systems, Santa Barbara, CA). EEG signals were amplified, band-pass filtered (0.5–35 Hz) and digitized at 500 Hz.

Sleep stages (wake, stage 1, stage 2, SWS and REM) were scored using 30-s epochs by an experienced scorer by visual analysis of the sleep recordings, in accord with standardized criteria [24]. The following sleep parameters were defined: total sleep time (TST; min), sleep onset latency (SOL; min), wake time after sleep onset (WASO; min), sleep efficiency (SE; %), REM latency (min) and amount of each sleep stage (stage 1, stage 2, SWS and REM; min).

Cardiovascular measures

An electrocardiogram (ECG) was recorded through 1-cm diameter Ag/AgCl spot electrodes in a modified Lead II Einthoven configuration. The signal was acquired on a BIOPAC MP100 acquisition system (BIOPAC Systems, Santa Barbara, CA), amplified, band-pass filtered (1–100 Hz) and digitalized at 500 Hz. The R-waves were automatically detected by a digital trigger and IBIs were computed by the software. Subsequently, the detection of R-waves was visually checked and manually adjusted. A third-order polynomial filter for detrending was applied to remove trend components and power spectrum analysis of the HRV (using the Fast Fourier Transformation method) was conducted on 2-min artifact-free windows selected across all night, to estimate spectra of very low (VLF [ms^2]; range 0–0.04 Hz), low (LF [ms^2]; range 0.04–0.15 Hz) and high (HF [ms^2]; range 0.15–0.4 Hz) frequencies by Kubios HRV Analysis Software 2.0 (MATLAB, Kuopio, Finland). The selected epochs were free from sleep stage changes and only wake prior to the sleep onset was detected. Data were then averaged for each stage of sleep across all night. The following variables were calculated: HF normalized units (HF [ms^2]/(total power [ms^2] – VLF [ms^2])), LF normalized units (LF [ms^2]/(total power[ms^2] − VLF [ms^2])) and LF/HF ratio (LF [ms^2]/HF [ms^2]), indexes of sympathovagal balance (high sympathovagal balance indicates sympathetic dominance; low sympathovagal balance indicates parasympathetic dominance). Considering that HF normalized units (HF n.u.) and LF normalized units (LF n.u.) are complementary, only HF n.u. and LF/HF ratio have been reported in the results (for further details please refer to "Discussion").

Cardiac impedance measures were calculated online by 30-s ensemble averages collected through Impedance Cardiograph Minnesota model 304B (IFM, Greenwich, CT) and then averaged off-line for each sleep stage throughout the night (only wake prior to the sleep onset was considered). Four longitudinal aluminum band electrodes were placed in tetrapolar configuration according to the configuration reported in the guidelines [26]. A 4-mA AC current at 100 kHz was transmitted through the thorax between the outer electrodes and Z_0 (basal impedance), and dZ/dt (rate of change in the impedance waveform on a given beat) signals were estimated from the two inner electrodes.

Stroke volume (SV, blood pumped by the left ventricle with each heartbeat; ml) was obtained by applying the Kubicek equation. Cardiac output (CO, blood pumped by the left ventricle each minute; l/min) was derived by multiplying hear rate (HR, number of heartbeats per unit of time; bpm) by SV. Pre-ejection period (PEP, considered to be inversely related to sympathetic beta-adrenergic activity; ms) was calculated for each cardiac cycle as the time interval from the beginning of the electrical systole, the Q wave on the ECG signal to the opening of the aortic valve and the B point on the dZ/dt signal [26]. Each cardiac cycle was visually checked and the positions of points B and X in the dZ/dt signal and Q peak in the ECG were manually adjusted where necessary.

Data analyses

A 2 (between groups: insomniacs and good sleepers) × 5 (within sleep stages: wake, stage 1, stage 2, SWS and REM) mixed-design ANOVA was applied to the mean values of each cardiovascular variable.

Newman–Keuls post hoc comparisons were used on the significant effects and the Huynh–Feldt (H–F) correction was applied. Uncorrected degrees of freedom, epsilon values (ε) and corrected probability levels were recorded. Partial eta-squared (η_p^2) has been reported as a measure of the effect size.

In addition, Pearson's correlations were performed to investigate the association between subjective scores of PSQI and AIS, SE and each cardiovascular index averaged over all night.

For all statistical analyses, the probability level was set at $p < 0.05$ for significance.

Results

Descriptive variables

Insomniacs and good sleepers did not show differences in age or BMI. Scores of PSQI and AIS were higher in insomniacs as expected. Furthermore, insomniacs reported significantly higher levels of hyper-arousal compared with good sleepers (Table 1).

Sleep parameters

Insomniacs had a lower sleep quality (reduced SE as well as, a consequence of the same TIB, a lower TST). They also had higher WASO in comparison to controls (Table 2).

Table 1 Means and SD of descriptive and subjective variables

	Insomniacs	Good sleepers	*t*
Age (year)	23. 00 (2.40)	23.56 (3.17)	−0.42
BMI (kg/m^2)	21.83 (3.37)	22.07 (2.58)	−0.17
Length of insomnia (year)	4. 00 (3.12)		
PSQI	9. 67 (1.22)	4.44 (2.90)	4.95***
AIS	10.00 (3.16)	2.22 (1.92)	6.31***
HS	44. 56 (4.03)	30.67 (5.85)	5.86***

AIS Athens Insomnia Scale, *BMI* body mass index, *HS* Hyperarousal Scale, *PSQI* Pittsburgh Sleep Quality Index

*** $p < 0.001$

Table 2 Means and SD of sleep parameters

	Insomniacs	Good sleepers	*t*
SE (%)	91 (5)	96 (3)	−2.78*
TST (min)	436 (23)	460 (12)	−2.78*
SOL (min)	18 (14)	9 (6)	1.87
WASO (min)	26 (18)	12 (8)	2.19*
REM latency (min)	83 (44)	97 (36)	−0.73
REM (min)	78 (24)	83 (13)	−0.47
Stage 1 (min)	52 (23)	55 (16)	−0.30
Stage 2 (min)	223 (36)	221 (26)	0.18
SWS (min)	82 (47)	102 (23)	−1.13

REM rapid eye movement, *SE* sleep efficiency, *SOL* sleep onset latency, *SWS* slow wave sleep, *TST* total sleep time, *WASO* wake after sleep onset

* $p < 0.05$

Cardiovascular indexes

PEP was faster in insomniacs over the whole night (group main effect: $F_{1,\ 16} = 6.08$, $p < 0.05$, $\eta_p^2 = 0.27$). In addition, PEP was faster in wake and in SWS compared to stage 1, stage 2 and REM in both groups (sleep stage main effect: $F_{4,\ 64} = 5.87$, $p < 0.001$, $\eta_p^2 = 0.27$, $\varepsilon = 0.75$) (Fig. 1). HR was lower in stage 1, stage 2 SWS and REM compared to wake, and in stage 2 compared to REM in insomniacs, but not in controls (group × sleep stage interaction: $F_{4,\ 64} = 3.71$, $p < 0.01$, $\eta_p^2 = 0.19$, $\varepsilon = 0.72$) (Fig. 2). SV was significantly lower in insomniacs, as indicated by a group main effect ($F_{1,\ 16} = 7.84$, $p < 0.05$, $\eta_p^2 = 0.33$). Moreover, both groups showed a lower SV in REM compared to wake, stage 1, stage 2 and SWS (sleep stage main effect: $F_{4,\ 64} = 4.44$, $p < 0.01$, $\eta_p^2 = 0.22$, $\varepsilon = 0.76$), and a reduction in CO during stage 1, stage 2, SWS and REM compared to wake (sleep stage main effect: $F_{4,\ 64} = 14.96$, $p < 0.001$, $\eta_p^2 = 0.48$, $\varepsilon = 0.80$).

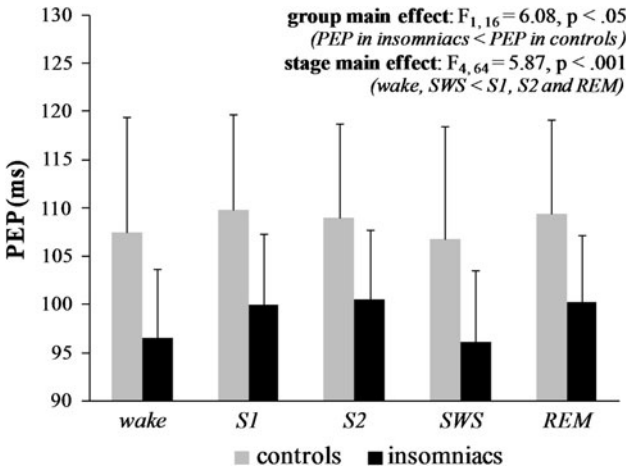

Fig. 1 Mean and SD of pre-ejection period (PEP) values across sleep stages (wake; stage 1, S1; stage 2, S2; slow wave sleep, SWS; rapid eye movement sleep, REM) in insomniacs and good sleepers

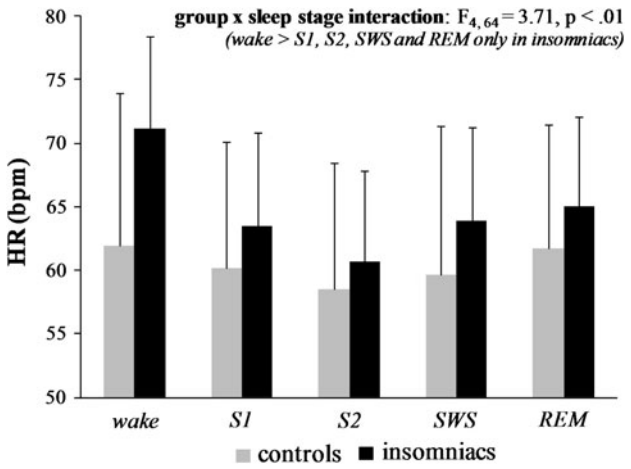

Fig. 2 Mean and SD of heart rate (HR) values across sleep stages (wake; S1, stage 1; S2, stage 2; SWS, slow wave sleep; REM, rapid eye movement sleep) in insomniacs and good sleepers

HF n.u. was higher in SWS and stage 2 in comparison to wake, stage 1 and REM in insomniacs as well as in good sleepers (sleep stage main effect: $F_{4,\ 64} = 38.02$, $p < 0.001$, $\eta_p^2 = 0.70$, $\varepsilon = 0.55$). Similarly, LF/HF ratio was lower in stage 2 and SWS compared to REM, stage 1 and wake in both groups (sleep stage main effect: $F_{4,\ 64} = 18.40$, $p < 0.001$, $\eta_p^2 = 0.53$, $\varepsilon = 0.62$). Means and standard deviations for the autonomic measures are provided in Table 3.

Pearson's correlations

Reduced percentages of SE were associated with higher subjective scores of AIS ($r = -0.55$, $p < 0.05$) and HS ($r = -0.51$, $p < 0.05$) (Fig. 3). In addition, PEP was

Table 3 Means and SD of the autonomic measures across stages of sleep

	Wake	REM	Stage 1	Stage 2	SWS
PEP (ms)					
Insomniacs	96.47 (4.65)	100.21 (5.65)	99.91 (4.64)	100.54 (4.50)	96.18 (4.96)
Controls	107.49 (10.44)	109.40 (11.48)	109.79 (11.74)	108.88 (11.72)	106.76 (12.01)
HR (bpm)					
Insomniacs	71.10 (7.24)	65.06 (6.99)	63.47 (3.35)	60.70 (7.09)	63.85 (7.44)
Controls	61.92 (12.01)	61.77 (9.71)	60.18 (9.91)	58.56 (9.92)	59.67 (11.70)
Total power (ms^2)					
Insomniacs	4562 (2673)	11543 (9563)	10224 (8281)	5142 (5667)	4562 (2673)
Controls	4797 (3281)	6431 (7449)	7484 (4866)	4892 (3327)	4797 (3281)
LF (ms^2)					
Insomniacs	1461 (936)	4345 (3553)	4933 (4335)	3425 (2808)	1230 (1065)
Controls	1847 (1929)	2761 (3232)	3965 (1708)	1664 (1163)	911 (850)
HF (ms^2)					
Insomniacs	1578 (1288)	4683 (4520)	5894 (6738)	5491 (4854)	3470 (4542)
Controls	1101 (866)	2099 (3206)	1792 (1094)	2278 (1852)	2311 (2288)
HF n.u.					
Insomniacs	0.50 (0.13)	0.48 (0.10)	0.49 (0.15)	0.59 (0.11)	0.69 (0.12)
Controls	0.39 (0.14)	0.38 (0.09)	0.38 (0.09)	0.56 (0.09)	0.70 (0.10)
LF/HF ratio					
Insomniacs	1.24 (0.97)	1.18 (0.51)	1.30 (1.03)	0.76 (0.39)	0.50 (0.32)
Controls	1.72 (0.66)	1.80 (0.72)	1.80 (0.69)	0.82 (0.29)	0.45 (0.19)

HF high frequency, *HR* heart rate, *LF* low frequency, *PEP* pre-ejection period, *REM* rapid eye movement, *SWS* slow wave sleep

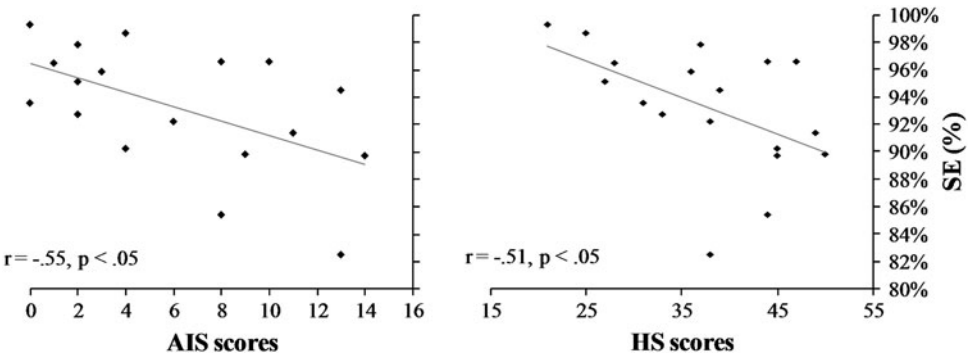

Fig. 3 Graphical representation of the association between sleep efficiency (SE) and Athens Insomnia Scale (AIS) and Hyperarousal Scale (HS) scores

negatively associated with AIS ($r = -0.53$, $p < 0.05$) and PSQI ($r = -0.58$, $p < 0.05$) scores (Fig. 4).

Discussion

A significant constant sympathetic hyper-activation characterized the insomniacs' night, as they showed faster PEP, i.e., a higher beta-adrenergic sympathetic activity, during all stages of sleep. This result suggests that an abnormal autonomic balance plays a key role in this condition and strongly supports the association between insomnia and increased cardiovascular risk [21, 22, 30]. In addition, PEP was directly associated with subjective sleep quality assessed by PSQI and AIS, so that individuals who subjectively reported poor sleep showed high nocturnal sympathetic activation. PSG sleep efficiency was also negatively associated with perceived sleep quality and arousal, so that individuals who subjectively reported poor

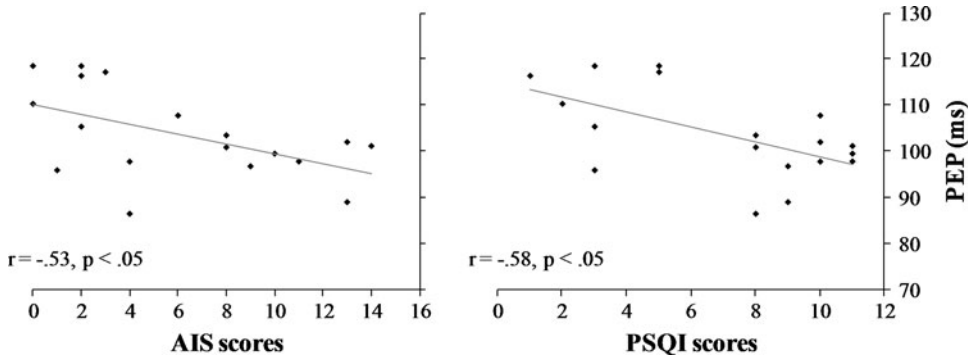

Fig. 4 Graphical representation of the association between pre-ejection period (PEP) and Athens Insomnia Scale (AIS) and Pittsburgh Sleep Quality Index (PSQI) scores

sleep or elevated perceived arousal showed poor objective sleep efficiency. Further investigations are required to assess the predictive role of these subjective variables in determining objective sleep quality and physiological cardiac sympathetic activation.

PEP was significantly faster in wakefulness compared to REM, stage 1 and stage 2 both in controls and insomniacs, suggesting a decrease of sympathetic involvement through the night, although PEP values were paradoxically comparable in wake and SWS. The absence of increased PEP values in SWS is inconsistent with previous findings highlighting reduced sympathovagal balance across the night [34]. However, it is likely that PEP values were influenced by changes in blood pressure (BP) [38]. Reductions in BP decrease PEP, and, as BP falls dramatically at sleep onset [35], this likely caused a decrease in PEP at the time SWS was most abundant. Thus, the lower PEP in SWS may be secondary to a fall in BP rather than reflecting sympathetic activation.

Comparing wakefulness with the other sleep stages, only insomniacs showed a reduction in heart rate (−12.37 %), which was elevated in insomniacs throughout the night, albeit at nonsignificant level. Based on previous results showing increases of HF from wake to sleep across the sleep onset period only in insomniacs [13], we might speculate that the HR reduction from wake to sleep in insomniacs, in association with a constantly faster PEP observed across all night, reflects a co-activation of the two autonomic branches of the neurovegetative system and suggests that converging pathways play a key role in the pathophysiology of primary insomnia.

Consistent with the literature [20, 38], in our data insomniacs and control individuals showed a decrease in cardiovascular activity across the night (reduction in cardiac output and increase in PEP values). Further, in agreement with studies on healthy subjects [2, 5, 35, 39] as well as on insomnia patients [3, 19], HRV variables showed a reduction in sympathovagal balance from wake to deep sleep, in both groups.

Significantly lower stroke volume associated with elevated HR in insomniacs (even if not significant) and comparable cardiac output among groups suggested in insomniacs a sympathetic activation of the heart, but not a different nocturnal metabolism [27]. This finding might be cautiously interpreted in light of the results by Nofzinger and colleagues [23] of an elevated global cerebral glucose metabolism during sleep and awake in insomniacs compared to healthy subjects. However, this issue needs to be clarified by further studies.

Despite several studies demonstrating an association between NREM sleep and enhanced vagal tone compared with wakefulness, the effect of sympathetic nervous system on the heart during sleep remains unclear [34]. Keeping in mind that PEP is an index assessing sympathetic control on the heart, only a small number of studies have evaluated PEP during the night, with inconclusive results [5–7, 35, 36], suggesting that further studies examining the autonomic variations during sleep should focus on this index.

In spite of the disagreement in scientific community about the mathematical and physiological meaning and interpretation of the normalized frequency domain-HRV indexes, some considerations seem to be appropriate. HF n.u. and LF n.u. reciprocally vary from 0 to 1 and should be considered complementary; furthermore, both are correlated to the LF/HF ratio which may theoretically vary from 0 to infinity. However, although these variables are redundant, we reported both HF normalized unit and the ratio, considering them as a single dimension of information reflecting the sympathovagal balance, as proposed by Burr and colleagues [8]. In addition, to control for a potential confounding role of respiration in the outcome of HRV measures, we detected the peak (Hz) in the high-frequency band during wake and we failed to find any group differences ($p = 0.82$).

Despite polysomnography not being indicated for the routine evaluation of primary insomnia and considering that sleep parameters failed to show large group differences, a remark about polysomnography data of our sample seems to be necessary. The mean percentage of sleep

efficiency was higher and the mean sleep onset latency was lower in insomniacs with respect to the limits commonly considered normal by sleep experts. When subjective estimations of sleep parameters are compared with objective polysomnography data, insomniacs are inclined to underestimate their sleep quality, and when differences are large, patients are considered to suffer from sleep state misperception; nevertheless, subjects are considered insomniacs if they report SOL $>$ 30 min, TST $<$ 6.5 h and SE $<$ 85 %. Such inconsistency might be due to the fact that the condition of insomnia is variable from night to night and insomniacs were enrolled according to DSM-IV [1] criteria without polysomnographic exclusion criteria.

The main limitation of the present study is the small sample size. Over 400 undergraduates have been screened in our study to find only 11 insomniacs (two insomniacs had to be rejected for technical reasons). This limitation was mainly due to the low impact of primary insomnia in the general population, the young participants and the restricted criteria used to recruit the insomnia group (insomniacs had to satisfy the DSM-IV criteria for the primary insomnia and also to report a history of insomnia for at least 1 year).

Summarizing, our study described the nocturnal cardiovascular pattern in primary insomnia adding new information on the general hyper-activation hypothesized as underlying this condition. Our results show that primary insomnia is characterized by a constant cardiac sympathetic nocturnal hyper-activation correlated to a poor perceived sleep quality that, in turn, is related to a higher self-reported hyper-arousal.

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Conflict of interest The authors declare that they have no conflict of interest.

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