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Poor sleep quality is associated with cardiac autonomic dysfunction in treated hypertensive men

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Keywords:	Sleep, hypertension, heart rate variability, baroreflex sensitivity, autonomic nervous system
Abstract:	Hypertensives present cardiac autonomic dysfunction. Reduction in sleep quality increases blood pressure (BP) and is associated with hypertension. Previous studies suggested a relationship between cardiovascular autonomic dysfunction and sleep quality; but it is unclear whether this association is present in hypertensives. Thus, this study evaluated the relationship between sleep quality and cardiac autonomic modulation in hypertensives. Forty-seven middle-aged hypertensive men under consistent anti-hypertensive treatment were assessed for sleep quality by the Pittsburgh Sleep Quality Index (PSQI - higher score means worse sleep quality). Additionally, their beat-by-beat BP and heart rate (HR) were recorded, and cardiac autonomic modulation was assessed by their variabilities. Mann-Whitney and T-tests were used to compare different sleep quality groups: poor (PSQI >5, n=24) vs. good (PSQI ≤5, n=23), and Spearman's correlations to investigate associations between sleep quality and autonomic markers. Patients with poor sleep quality presented lower cardiac parasympathetic modulation

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	<p>(HR high frequency band = 26 ± 13 vs. 36 ± 15 nu, $P = .03$; HR total variance = 951 ± 1373 vs. 1608 ± 2272 ms², $P = .05$) and cardiac baroreflex sensitivity (4.5 ± 2.3 vs. 7.1 ± 3.7 ms/mmHg, $P = .01$). Additionally, sleep quality score presented significant positive correlation with HR ($r = +0.34$, $P = .02$) and negative correlations with HR high frequency band ($r = -0.34$, $P = .03$), HR total variance ($r = -0.35$, $P = .02$) and cardiac baroreflex sensitivity ($r = -0.42$, $P = .01$), showing that poor sleep quality is associated with higher HR and lower cardiac parasympathetic modulation and baroreflex sensitivity. In conclusion, in treated hypertensive men, poor sleep quality is associated with cardiac autonomic dysfunction.</p>



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Abstract

Hypertensives present cardiac autonomic dysfunction. Reduction in sleep quality increases blood pressure (BP) and is associated with hypertension. Previous studies suggested a relationship between cardiovascular autonomic dysfunction and sleep quality; but it is unclear whether this association is present in hypertensives. Thus, this study evaluated the relationship between sleep quality and cardiac autonomic modulation in hypertensives. Forty-seven middle-aged hypertensive men under consistent anti-hypertensive treatment were assessed for sleep quality by the Pittsburgh Sleep Quality Index (PSQI - higher score means worse sleep quality). Additionally, their beat-by-beat BP and heart rate (HR) were recorded, and cardiac autonomic modulation was assessed by their variabilities. Mann-Whitney and T-tests were used to compare different sleep quality groups: poor (PSQI >5, n=24) vs. good (PSQI ≤5, n=23), and Spearman's correlations to investigate associations between sleep quality and autonomic markers. Patients with poor sleep quality presented lower cardiac parasympathetic modulation (HR high frequency band = 26 ± 13 vs. 36 ± 15 nu, $P = .03$; HR total variance = 951 ± 1373 vs. 1608 ± 2272 ms², $P = .05$) and cardiac baroreflex sensitivity (4.5 ± 2.3 vs. 7.1 ± 3.7 ms/mmHg, $P = .01$). Additionally, sleep quality score presented significant positive correlation with HR ($r = +0.34$, $P = .02$) and negative correlations with HR high frequency band ($r = -0.34$, $P = .03$), HR total variance ($r = -0.35$, $P = .02$) and cardiac baroreflex sensitivity ($r = -0.42$, $P = .01$), showing that poor sleep quality is associated with higher HR and lower cardiac parasympathetic modulation and baroreflex sensitivity. In conclusion, in treated hypertensive men, poor sleep quality is associated with cardiac autonomic dysfunction.

Key words: Sleep, hypertension, heart rate variability, baroreflex sensitivity, autonomic nervous system

Introduction

Hypertension affects about 1 billion adults and is responsible for 13% of the deaths worldwide¹. This unfavorable framework may be partially caused by the cardiovascular autonomic dysfunction present in hypertension¹. Hypertensives are known to have reduced baroreflex sensibility², which leads to increased cardiac sympathovagal balance and sympathetic vasomotor modulation³. Additionally, autonomic dysfunction in hypertension is associated with increased risk for target-organ damage⁴ and the occurrence of cardiovascular events⁵. Thus, to identify factors associated with cardiovascular autonomic dysfunction in hypertension can help the disease treatment and control.

Along this line, sleep quality seems to play an important role in BP control⁶ with short sleep duration or poor sleep efficacy being associated with hypertension developing⁷. Sleep deprivation increases BP by changing cardiovascular autonomic modulation, mainly impairing baroreflex control and increasing cardiac sympathovagal balance⁸. Additionally, higher BP levels have been reported in subjects with poor sleep quality⁹. However, all these findings derived from studies with normotensives, being important to investigate whether sleep quality is also associated with cardiovascular autonomic dysfunction in hypertensives, who may already present autonomic dysfunction and receive anti-hypertensive medications.

Therefore, the aim of this study was to evaluate whether sleep quality is associated with cardiovascular autonomic dysfunction in treated hypertensive patients. The hypothesis is that poor sleep quality is also associated with cardiovascular autonomic dysfunction in this population.

Methods

Subjects

This study investigated hypertensive men receiving anti-hypertensive drugs consistently for at least four months. To take part in the study, the subjects had to present the

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3 following criteria: i) male; ii) aging between 30-65 years old; iv) essential hypertension with
4 no target-organ damage; v) resting systolic (SBP) and diastolic (DBP) lower than 160 and 105
5 mm Hg, respectively; vi) body mass index (BMI) ≤ 35 kg/m²; vii) neither chronotype (i.e.
6 Horne and Ostberg's questionnaire scores between 42 and 58)¹⁰; viii) exercise practice once a
7 week or lower; vi) not using insulin or medications that directly affects cardiac autonomic
8 modulation (i.e. non-dihydropyridine calcium channel antagonists or beta-blockers); and ix)
9 without any cardiovascular abnormality in resting or exercise electrocardiograms (ECG).

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19 Data for this study derived from a bigger study that was approved by the Research
20 Ethical Committee of the School of Physical Education and Sport of the University of São
21 Paulo (n° 966.072) and was registered at the Brazilian Clinical Trials
22 (www.ensaiosclinicos.gov.br - RBR-7q7pz7). For all procedures, this study followed the
23 principles in the Declaration of Helsinki.

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Subjects who agreed in participating signed the informed consent. The following preliminary exams were conducted. Personal data, medical history (including diagnosis of any sleep disorder), medication use, and physical activity habits were checked by an interview with a physician. Auscultatory BP was measured at rest using a mercury sphygmomanometer (Uniteq, São Paulo, Brazil) in accordance with guidelines^{1, 11}. Body weight and height were assessed using a scale (Filizola S.A, Personal, Campo Grande, Brazil), and BMI was calculated. Chronotype category was determined using Horne & Ostberg's questionnaire¹⁰. Absences of secondary hypertension and target-organ damage were confirmed through clinical exams¹¹. ECG abnormalities were checked by a physician at rest and during a maximal cycle ergometer exercise test¹².

Study design

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3 This is a cross-sectional observational study carried out between February 2015 and
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5 November 2016. After preliminary exams, all subjects who fulfilled the study criteria visited
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7 the laboratory twice within an interval of 2-7 days. Data collection was always conducted
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9 between 7 and 9 a.m. to avoid any influence of circadian rhythms, and assessments were
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11 conducted in a controlled temperature room (20-22°C).
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15 In the first visit, the subjects fulfilled the sleep quality questionnaire assisted by a
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17 researcher to solve any doubt. Sleep quality was measured by the Pittsburgh Sleep Quality
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19 Index (PSQI) that reports perception about sleep quality. This questionnaire has a high test-
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21 retest reproducibility (Cronbach's alpha > 0.80¹³), and an intraclass correlation coefficient of
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23 0.87¹⁴. Its score varies from 0 (best quality) to 21 (worst quality), and the clinical cutoff
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25 point is 5 (i.e. "poor" sleepers when PSQI is > 5 and "good" sleepers when PSQI is ≤ 5)¹⁵.
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27 The questionnaire's sensitivity (98.7%) and specificity (84.4%) are high for identifying sleep
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29 disorders using the cut-off score 5¹⁴.
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33 For the second visit, the subjects were instructed to: 1) arrive to the laboratory after an
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35 overnight fast; 2) avoid physical effort and alcoholic beverages for the previous 24 hours and
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37 caffeinated products for the previous 12 hours; and 3) take their anti-hypertensive medications
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39 at regular time, as usual. After arriving, they received a standardized meal composed by 50 ml
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41 of juice and 2 cereal bars and waited 30 min for beginning of the experiments. Then, they
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43 seated on a comfortable chair and after 10 min, heart rate (HR), beat-to-beat BP and respiratory
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45 signals were collected for 10 min. Beat-to-beat BP was assessed by photoplethysmography
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47 (Finapres Medical System, Arnhem, Netherlands), HR by ECG (EMG System do Brazil, EMG,
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49 030110/00B, São Paulo, Brazil) and respiratory movements by a thoracic piezoelectric belt
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51 (UFI, Pneumotrace2, Morro Bay, USA). Cardiovascular autonomic modulation was evaluated
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53 by the spectral analysis of HR and BP variability. For that, R-R interval, beat-by-beat BP, and
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55 respiratory signals were recorded through a data acquisition system (Windaq, Dataq
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Instruments, Akron, Ohio, USA) using a sample rate of 500 Hz per channel. Afterwards, data was analyzed by a specific software (Heart Scope II, v. 1.3.0.1, A.M.P.S. LLC, New York, USA) in stationary segments of 300 beats. HR and BP values were calculated by the mean value obtained in the chosen stationary period. Spectral analysis employed the autoregressive method, and the oscillatory components of the time series were modeled by the Levinson-Durbin recursion with the model order chosen according to the Akaike's criterion¹⁶. Low (LF_{RR}: 0.04-0.15 Hz) and high-frequency (HF_{RR}: 0.15-0.4 Hz) bands of HR variability were expressed as normality units (nu). As proposed by the Task Force¹⁷, LF_{RR} nu was accepted as a marker of predominant cardiac sympathetic modulation, HF_{RR} nu and total variance (TV_{R-R}) as markers of cardiac parasympathetic modulation, and LF/HF as cardiac sympathovagal balance. Vasomotor sympathetic modulation was assessed by the absolute value of low frequency band of SBP variability (LF_{SBP}), and cardiac spontaneous baroreflex sensitivity (cSBR) was calculated using the sequence technique as previously described¹⁸.

Statistical analysis

Data distribution was checked by Shapiro-Wilk test (IBM SPSS for windows, Illinois, USA). Differences between "good" and "poor" sleepers were analyzed, respectively, by t-tests or Mann-Whitney tests depending on the presence or not of a normal data distribution. Since PSQI global score presented non-normal distribution, Spearman correlations were carried out to analyze the relationship between sleep quality and cardiovascular autonomic markers. Data are shown in mean±standard deviation, and a value of $P \leq .05$ was set as significant.

Results

Forty-seven hypertensive men fulfilled the study criteria and participated in the present study. None of them reported diagnosis of any sleep disorder. Twenty-four subjects

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3 were classified as poor sleepers and twenty-three as good sleepers. Despite sleep quality, all
4 other anthropometric and clinical characteristics as well as medication use were similar
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6 between the two groups (Table 1).
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12 *** Table 1 is about here**
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17 Comparisons between the groups are shown in Figure 1. SBP, DBP and HR were not
18 different between the poor and good sleeper groups (136±16 vs. 141±15 mmHg, 80±6 vs. 79±7
19 mmHg, and 76±9 vs. 72±9 bpm, respectively, all $P > .05$). HF_{R-R} and TV_{R-R} were lower in the
20 poor than the good sleeper group (26±13 vs. 36±15nu, $P = .03$; and 951±1373 vs. 1608±2272
21 ms^2 $P = .05$), while LF_{R-R} and LF/HF were similar between them (57±21 vs. 57±20 nu, 3.8±3.7
22 vs. 2.7±3.5, respectively, all $P > .05$). No difference was observed for LF_{SBP} (13.6±17.5 vs.
23 10.8±9.7 mmHg², $P > .05$), while cBRS was lower in the poor than the good sleeper group
24 (4.5±2.3 vs. 7.1±3.7 ms/mmHg, $P = .01$).
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38 *** Figure 1 is about here**
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42 Correlations between sleep quality score and cardiovascular autonomic markers are
43 shown in Figure 2. SBP, DBP, LF_{R-R} , LF/HF and LF_{SBP} did not present significant correlations
44 with PSQI. HR was positively associated with PSQI ($r = +0.34$, $P = .02$), while TV_{R-R} , HF_{RR} and
45 cBRS presented significant negative correlations with PSQI ($r = -0.35$, $P = .02$; $r = -0.34$, $P = .03$;
46 and $r = -0.42$, $P = .01$, respectively).
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Discussion

The main finding of the current study is that poor sleep quality is associated with impaired cardiac parasympathetic modulation and lower cardiac baroreflex sensitivity in treated middle-age hypertensive men, which corroborates with the hypothesis of the study.

Since a higher score in the PSQI represents lower sleep quality, the positive correlation found between PSQI and HR in addition to the negative correlations with TV_{R-R} , HF_{R-R} and cBRS show that subjects with worse sleep quality presented higher HR and lower TV_{R-R} , HF_{R-R} , and cBRS. These results are coherent with the differences observed between the poor and the good sleeper groups for HF_{R-R} , TV_{R-R} and cBRS. As TV_{R-R} and HF_{R-R} are mainly markers of cardiac parasympathetic modulation¹⁷, the correlations observed with these variables show that poor sleep quality is associated with impaired parasympathetic control of HR. Despite the association between sleep quality and HR variability indices, no relationship was detected with LF_{SBP} . As this index is mainly a maker of vasomotor sympathetic modulation¹⁹, this result is coherent with the association of sleep quality mainly with parasympathetic markers.

The mechanisms behind the association between poor sleep quality and impaired cardiac parasympathetic modulation were not assessed in the present study, but some putative mechanistic pathways may be raised. Poor sleep quality is usually associated with arousals that disrupt sleep autonomic pattern²⁰, decreasing parasympathetic and increasing sympathetic activity, HR and BP during sleep²¹. Chronically, these repetitive sleep disruptions may progressively lead to a persistent cardiovascular autonomic dysfunction¹⁹. Thus, the poor sleepers in the present study might present more arousals than the good sleepers, which may contribute to a worse autonomic dysfunction mainly characterized by lower cBRS and consequently impaired cardiac parasympathetic modulation.

The association between poor sleep quality and cardiac autonomic dysfunction has already been observed in healthy subjects⁹. The novelty of the present study was to show that

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3 this relationship is also present in subjects who already present autonomic dysfunction, such
4 as hypertensives, even when receiving anti-hypertensive medication. Actually, the mean value
5 of cBRS in the whole sample of this study (5.57 ± 3.26 ms/mmHg) was lower than observed in
6 healthy middle-aged men (9.9 ms/mmHg)²². Together, these appointments confirm the
7 presence of autonomic dysfunction in this population and show that it becomes worst in
8 patients who present poor sleep quality. Thus, sleep quality assessment may strengthen the
9 clinical management in hypertension.
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19 Additionally, the current results may have important clinical implications. It is known
20 that cardiovascular autonomic dysfunction is associated with poor cardiovascular prognosis¹⁸
21 with values of cBRS lower than <3 ms/mmHg increasing in 2.98% the relative risk of
22 cardiovascular mortality²³. Along this line, poor sleep quality has also been shown to increase
23 the risk of all causes and cardiovascular mortality²⁴. More interestingly, one study showed that
24 the association of poor sleep quality with high HR (a marker of autonomic dysfunction)
25 increases the risk of mortality even more than each factor alone²⁵. Based on this background,
26 it is possible to state that hypertensives with poorer sleep quality are at higher cardiovascular
27 risk. Thus, the adoption of treating strategies that besides decreasing BP also ameliorate sleep
28 quality may bring a better cardiovascular autonomic control and prognosis. Changes in
29 lifestyle, such as increase in physical activity and weight loss, have been shown to improve
30 cardiovascular autonomic control^{26, 27} and sleep quality²⁸. Thus, these non-pharmacological
31 treatments may be important for hypertension treatment also because they may act on a poorly
32 explored aspect of this disease highlighted in this study, the sleep quality.
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51 We acknowledge that this study results were limited to Horn and Ostberg's neither
52 chronotype type and middle-aged men. Extreme chronotypes might affect sleep quality²⁹;
53 women present a different cardiovascular autonomic control and sleep quality pre and post-
54 menopause^{30,31}; and both factors change with aging, presenting different relationships at each
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3 age group³². Additionally, subjects with obesity level 2 or greater were not included since
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5 high levels of obesity favor sleep disorders and cardiac autonomic dysfunction^{33, 34}, which
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7 may take to a misinterpret of the results regarding the associations within hypertension.
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9 Thus, caution should be taken when extrapolating the results to either extreme morningness
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11 or eveningness chronotypes, other age groups, subjects with BMI > 35 kg/m², and women.
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13 As a meaningful aspect, anti-hypertensive medication might be a confounder since some
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15 drugs are more likely to impact cardiovascular autonomic control³³. Taking this into account,
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17 subjects receiving beta-blocker and non-dihydropyridine calcium channel antagonists were
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19 not included in the study. Only beat-by-beat BP variability was assessed in the current study.
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21 Therefore, the absence of relationship between this BP variability index and sleep quality
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23 cannot be extrapolated to visit-to-visit or ambulatory BP variability indices that are
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25 strongly associated with poorer cardiovascular prognosis^{34, 35}. Sleep quality was measured
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27 using the PSQI, which differently from polysomnography (the gold-standard method to
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29 assess sleep)³⁶ is a subjective measure that does not allow to objectively assessing specific
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31 sleep parameters (e.g. duration, latency and efficiency) nor specific sleep abnormalities
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33 (e.g. obstructive sleep apnea) that may also have associations with autonomic dysfunction³⁶.
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35 Thus, future studies should address all these limitations, employing objective sleep
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37 measurements, studying other populations, measuring other variability indices, and
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39 assessing patients receiving specific anti-hypertensive medications.
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47 In conclusion, in treated middle-aged hypertensive men, poor sleep quality assessed by
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49 PSQI is associated with autonomic dysfunction mainly expressed by lower cardiac
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51 parasympathetic modulation and baroreflex sensitivity.
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54 55 56 **Acknowledgements**

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Conflict of interest

The authors declare no conflict of interest

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For Review Only

Figure Legends

Figure 1. Comparison between good and poor sleepers groups. Panel a) systolic blood pressure (SBP); b) diastolic BP (DBP); c) heart rate (HR); d) total variance of R-R interval variability (TV_{R-R}); e) normalized low-frequency component of R-R interval variability (LF_{R-R} nu); f) normalized high-frequency component of R-R interval variability (HF_{R-R} nu); g) low to high frequency ratio of R-R interval variability (LF/HF); h) low frequency component of systolic blood pressure variability (LF_{SBP}); and i) cardiac baroreflex sensitivity (cBRS). * Significantly different from good sleepers ($P < .05$).

Figure 2. Correlations between Pittsburgh Sleep Quality Index (PSQI) global score and a) systolic blood pressure (SBP); b) diastolic blood pressure (DBP); c) heart rate (HR); d) total variance of R-R interval variability (TV_{R-R}); e) normalized low-frequency component of R-R interval variability (LF_{R-R} nu); f) normalized high-frequency component of R-R interval variability (HF_{R-R} nu); g) low to high frequency ratio of R-R interval variability (LF/HF); h) low frequency component of systolic blood pressure variability (LF_{SBP}); and i) cardiac baroreflex sensitivity (cBRS). # Significant correlation ($P < .05$).

Table 1. Characteristics of the subjects

Variables	All subjects	Poor sleepers	Good sleepers
N	47	24	23
Age (years)	52±8	48±6	50±9
Height (m)	1.71±0.06	1.71±0.08	1.71±0.09
Weight (kg)	88.8±13.2	87.1±15.5	90.5±13.7
Body mass index (kg/m ²)	30.2± 3.8	29.6±3.9	30.7±3.3
Chronotype (score)	52±4	52±3	52±4
Sleep Quality (score)	6±3	4±1*	9±3
Hemodynamics			
Systolic BP (mmHg)	133±12	132±8	135±10
Diastolic BP (mmHg)	89±8	89±6	90±7
Hear rate (bpm)	76±10	76±10	76±9
Type of anti-hypertensive therapy			
One– n. (%)	35(74)	16(67)	16(70)
Two or more– n. (%)	12(26)	8(33)	7(30)
Anti-hypertensive drugs			
Angiotensin II receptor blockers – n. (%)	22(47)	11(46)	11(48)
Angiotensin-converting enzyme inhibitors – n. (%)	19(40)	10(42)	9(39)
Dihydropyridine calcium channel blockers– n. (%)	9(19)	4(16)	5(21)
Diuretics – n. (%)	10(21)	5(20)	5(21)

Values are mean±standard deviation; body mass index (the weight in kilograms divided by the square of the height in meters). * Significantly different from good sleepers (P>.05)

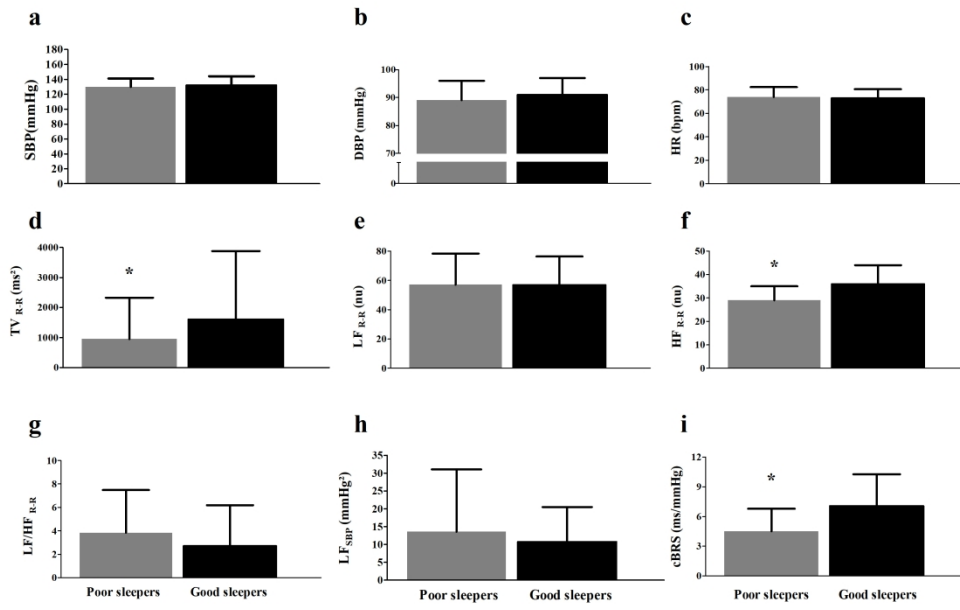


Figure 1

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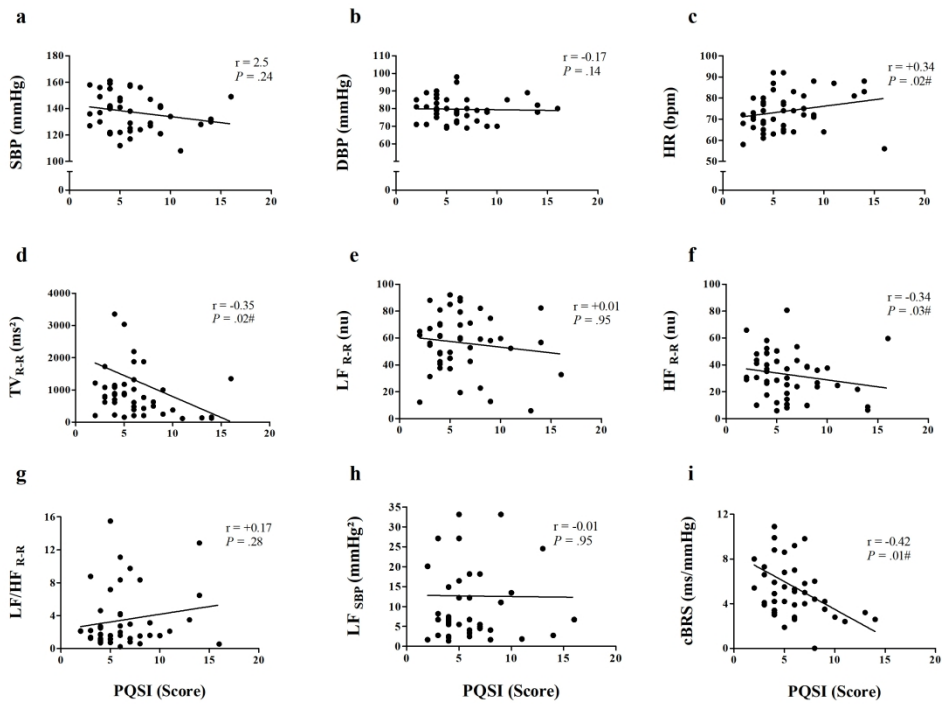


Figure 2

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