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Cardiovascular and autonomic consequences of sleep fragmentation

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ABSTRACT

Introduction: Sleep disruption is commonly found in normal individuals and those with sleep disorders. Risk factors for sleep fragmentation involve a combination of lifestyle, environmental, psychosocial factors and/or medical conditions. The main objective of this study was to analyse the impact of acute, induced sleep fragmentation upon autonomic cardiovascular regulation, measured by a non-invasive haemodynamic measurement technique.

Material and methods: The authors analysed beat-to-beat measurements of haemodynamic and autonomic parameters at 5-time points during sleep fragmentation: 9:00 a.m. (baseline), 9:00 p.m., 00:30 a.m., 4:00 a.m., and 7:30 a.m. Differences in the mean values for chronotropic parameters, cardiac contractility, parameters related to blood pressure regulation and workload of the left ventricle, and autonomic parameters were examined in seventeen healthy male volunteers. Direct results obtained from every time point were analysed using analysis of variance with repeated measures or the Friedman rank sum test.

Results: Sleep fragmentation had a significant negative impact on haemodynamic parameters related to cardiac contractility (SV $p < 0.001$, IC $p < 0.001$, HI $p < 0.001$); parameters related to workload of the left ventricle (CO $p < 0.001$, LVWI $p < 0.001$, ACI $p < 0.001$); parameters related to blood pressure regulation (sBP $p = 0.001$, TPR $p < 0.001$); on chronotropic parameters (HR $p < 0.001$, PEP $p < 0.001$, LVET $p < 0.001$) and an indicator of cardiac autonomic regulation: LF-RRI ($p = 0.001$).

Conclusions: Acute sleep fragmentation can modify haemodynamic control and autonomic cardiovascular regulation in healthy men; the most important changes were seen in the morning hours (4:00 a.m.). Therefore, conditions of chronic sleep fragmentation (e.g. shift work, uniformed services, clinicians), might lead to disturbance in the autonomic nervous system and therefore to problems with homeostasis in the cardiovascular system. Future research is needed in standardized conditions with large-scale studies to clarify the effects of chronic sleep fragmentation.

Key words: sleep loss; autonomic nervous system; cardiovascular; sleep deprivation

Introduction

Sleep plays an important role in brain function, metabolism and functioning of the cardiovascular, immune, or hormonal systems. Healthy sleep has good quality, sufficient duration, appropriate timing, and no disturbances or disorders. Sleep disruption is commonly found in both normal individuals and patients with sleep disorders and it is a substantial problem in modern society. Up to 70 million people in the US and ~45 million people in Europe have a chronic sleep disorder that impacts daily functioning and health [1]. Risk factors for sleep fragmentation or sleep deprivation involve a combination of lifestyle (e.g. shift work, jet lag, drinking alcohol, consuming excessive amounts of caffeine), environmental (e.g. excessive noise or light), psychosocial factors (e.g. anxiety, parents of young children) and/or medical condition (e.g. sleep disorders: obstructive sleep apnoea, insomnia, circadian rhythm disorders; diabetes, neurodegenerative diseases, pain) [2, 3].

What is important, poor sleep is associated with extreme psychological stress [1]. Apart from the aforementioned risk factors related to the individual and social situation, another important epidemiological factor that had an impact also upon sleep disturbances was the COVID-19 pandemic. Yuksel et al., [4] show that COVID-19-associated factors have impacted sleep health on a global level. They investigated changes in sleep patterns of 6882 participants across 59 countries and they reported, that about 30.7% of the participants sleeping less or much less than usual and 35.6% woke up during the night more or much more than usual, compared to pre-pandemic.

Chronobiology studies indicate that sleep disruption (fragmentation or deprivation) determines short and long-term health effects. Results of experimental studies [5] suggest that short-term consequences of sleep fragmentation are based on sympathetic activation with the haemodynamic, vasoconstrictive, and pro-thrombotic response, which affects the cardiovascular system and deteriorates its proper function [5]. These effects may also provide long-term consequences, in particular — cardiovascular events [6]. According to two cross-sectional studies on ca. 30000 and 404000 individuals sleep duration lower than 6 hours was significantly associated with increased risk of coronary heart disease (angina pectoris — OR = 1.32, $p < 0.005$) and myocardial infarction occurrence (OR = 1.21, $p < 0.001$) [7, 8]. Moreover, a study on rats has revealed, that sleep restriction after myocardial infarction (caused by left anterior descending coronary artery ligation) resulted in increased infarct size [9]. Apart from cardiovascular disease, other cross-sectional observational studies also suggest a relationship between short sleep duration or fragmentation and higher blood pressure, which resulted in an increased risk of hypertension [10, 11]. However, the conclusions are inconsistent, probably because of differences in the sample types and sizes, the duration of follow-up, the size of the effects, and some other variations in study design and exposure/outcome assessment [12]. The mechanisms responsible for cardiovascular dysfunctions induced by sleep deprivation are fairly known, however, there is some evidence that sleep deprivation induces inflammatory response (an increase of IL-6 and TNF- plasma levels in humans), endothelial dysfunction, oxidative stress, and abnormal lipid metabolism [13, 14]. Moreover, long-term consequences of sleep deprivation or fragmentation also result from increased activity of the sympathetic nervous system [15].

The main objective of this study was to analyse the impact of sleep fragmentation on haemodynamic and autonomic parameters, as well as heart contractility in healthy subjects. These parameters which reflect autonomic system status [e.g. pre-ejection period (PEP), left ventricular ejection time (LVET)] are measured by a non-invasive haemodynamic monitoring technique — Task Force Monitor (TFM). Such techniques are considered an alternative to invasive haemodynamic monitoring in intensive care units [16]. In the authors' opinion, this is the first study that evaluates heart contractility parameters after acute sleep fragmentation in laboratory conditions.

Material and methods

The authors assessed the haemodynamic profile and cardiac function in seventeen healthy male volunteers (age: 32.6 ± 2.6 years; BMI: 24.6 ± 2.9 kg/m^2), with current medical tests indicating the absence of disease (including routine laboratory tests). The main enrolment criteria included sex: male, no co-morbidity, no reported sleep disorders (Pittsburgh Sleep Quality Index < 5), and no extreme chronotype (ratings between 14 and 21 points on the morning-evening M/E questionnaire [17]). Exclusion criteria consisted of factors that could modify the response to sleep fragmentation: shift work, caffeine, alcohol, drugs dependence, participation in sports at a competitive level, alcohol consumption within 12 hours before the test, receiving any medication/supplements during the study and potential disorders of the cardiovascular system observed during the test. All potential study participants were questioned about their sleep quality, life habits and health state. Pre-test health state assessment of subjects included: basic neurological, clinical examination, and evaluation of the autonomic nervous system using the Autonomic Symptom Profile [18]. The study was approved by the Ethics Committee, Ludwik Rydygier Memorial Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Torun; written informed consent was obtained from all participants.

One week before the study (baseline week), the participants were requested to abstain from excessive caffeine (one caffeine-containing beverage per day at most) and alcohol consumption (< 5 alcoholic beverages per week). The entire study period was 2 nights. Subjects arrived at the laboratory in the evening for an 8h sleep adaptation episode. After the adaptive night, physical activity was restricted to a minimum, and subjects were not allowed to drink caffeine-containing liquids. Reading, writing, talking, and playing games were allowed during the experiment. Subjects ate the same meals at the same time of the day (8:00 a.m., 12:00 p.m., 3:00 p.m., 7:30 p.m.). Water (100 mL) was administered at hourly intervals during the protocol.

On the second night subjects remained in bed from 9:30 p.m. till 7:30 a.m. (semi-recumbent during wakefulness and supine during scheduled sleep episodes). Three

alternating sleep-wake cycles (or nap cycles, naps 1–3) of 150 min of scheduled wakefulness (light phase, < 8 lux) and 75 min of scheduled sleep (dark phase, 0 lux). The low-light intensity (< 8 lux) was chosen because it is below the threshold for suppressing melatonin secretion.

The examination was performed in the chronobiology laboratory while maintaining constant conditions (constant routine, temperature 22°C, humidity 60%, light < 10 lx). During the experiment, two investigators were present in the laboratory, and rotations of 12 hours were organized. Haemodynamic [heart rate (HR), blood pressure (BP), stroke volume (SV), cardiac output (CO), total peripheral resistance (TPR), thoracic fluid content (TFC)], heart contractility [index contractility (IC), acceleration index (ACI), Heather index (HI)], parameters of the left ventricle function [pre ejection period (PEP), left ventricular ejection time (LVET), left ventricular work index (LVWI)] and autonomic parameters [low frequency (LF), high frequency (HF), PSD] were automatically measured at rest (15 minutes after stabilization of the signals) with a Task Force Monitor — TFM (CNS Systems, Gratz, Austria). Task Force Monitor® is designed for non-invasive measurements of haemodynamic parameters and consists of electrocardiography (ECG), impedance cardiography (ICG), oscillometric (oscBP) and continuous (contBP) blood pressure measurement [19]. All measurements were obtained at 5 points during the study: 9:00 a.m. (baseline), 9:00 p.m., 00:30 a.m., 4:00 a.m., and 7:30 a.m.

Initially, 17 subjects were examined. However, due to the lack of data in some time points from two subjects, data from 15 subjects were analysed. Beat-to-beat data were filtered using Grubbs' test for outliers' elimination. Direct results obtained from every time point were included in the analysis process. Descriptive statistics are presented as mean ± standard deviation. Data on the impact of sleep deprivation were submitted to analysis of variance (ANOVA) with repeated measures and post hoc analysis using paired t-test and FDR correction of p-value was applied, if the assumption on normality was met. Effects size (omega squared (ω^2_p) and confidence interval (CI) (–95%; 95%) for effect size) were calculated. In the case of violation of the assumption of sphericity, then correction was applied. In the case of violation of normality assumption, the Friedman rank sum test was used, and post hoc analysis using Durbin-Conover with FDR adjustment of p-values. Effect size [Kendall's coefficient of concordance (WKendall)] and confidence interval (CI) (–95%; 95%) for *effect size* were calculated. Violin graphs and effect size calculation for both tests were done using R statistical package: ggstatsplot (ver. 0.6.5) [20] with a ggstatsplot library [Patil, I.; Powell, C. Ggstatsplot: 'ggplot2' Based Plots with Statistical Details. 2018. Available online: https://CRAN.R-project.org/package=ggstatsplot (accessed on 17 March 2021)].

Results

Table 1, 2, and figures 1–5 shows the mean results of cardiovascular and autonomic parameters during the study.

Table 1. Haemodynamic, heart contractility parameters change in baseline and during the sleep fragmentation

Parameter [unit]	01 Mean ± SD	02 Mean ± SD	03 Mean ± SD	04 Mean ± SD	05 Mean ± SD	P-value
HR [bpm]	63.3 ± 5.7	58.4 ± 5.1	56.5 ± 4.7	55.6 ± 5.0	61.7 ± 5.6	p < 0.001
SV [mL]	122.2 ± 13.0	119 ± 12.1	110.1 ± 16.5	97.7 ± 17.3	111.9 ± 15.8	p < 0.001
CO [L/min]	7.7 ± 1.1	7.0 ± 0.9	6.2 ± 1.1	5.4 ± 1.0	6.9 ± 1.4	p < 0.001
sBP [mmHg]	124.5 ± 9.5	128.5 ± 8.9	124.0 ± 7.5	121.4 ± 7.3	124.3 ± 7.9	0.001
dBP [mmHg]	79.2 ± 7.4	81.9 ± 8.5	79.3 ± 7.7	79.4 ± 8.1	79.6 ± 7.2	0.3
mBP [mmHg]	93.0 ± 8.4	95.7 ± 8.9	92.4 ± 7.8	92.6 ± 7.8	93.1 ± 6.9	0.1
TPR [dyne*s/cm^5]	960.8 ± 192.6	1095.9 ± 223.6	1217.7 ± 306.7	1393.5 ± 342.3	1094.6 ± 239.7	p < 0.001
PEP [ms]	106.5 ± 13.9	108.6 ± 13.7	113.1 ± 11.4	119.1 ± 8.0	110.5 ± 11.8	p < 0.001
HI [1/s^2]	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	p < 0.001
IC [1000/s]	71.7 ± 16.7	68.5 ± 18.2	60.8 ± 18.6	51.8 ± 16.1	63.1 ± 15.8	p < 0.001
ACI [100/s^2]	96.3 ± 24.8	96.7 ± 28.5	85.0 ± 25.7	72.0 ± 22.4	84.6 ± 21.3	p < 0.001
LVWI [mmHg*L/(min*m^2)]	4.7 ± 0.8	4.4 ± 0.6	3.8 ± 0.7	3.3 ± 0.6	4.2 ± 0.8	p < 0.001
LVET [ms]	317.5 ± 10.3	325.5 ± 4.6	331.0 ± 5.9	329.9 ± 10.5	321.8 ± 9.5	p < 0.001

ACI — acceleration index; CO — cardiac output; dBP — diastolic blood pressure; HI — Heather index; HR — heart rate; IC — index of contractility; LVET — left ventricular ejection time; LVWI — left ventricular work index; mBP — mean blood pressure; PEP — pre ejection period; sBP — systolic blood pressure; SV — stroke volume; TFC — thoracic fluid content; TPR — total peripheral resistance index

Table 2. Autonomic parameters' changes in baseline and during the sleep fragmentation

Parameter	01 Mean ± SD	02 Mean ± SD	03 Mean ± SD	04 Mean ± SD	05 Mean ± SD	P-value
LF-RRI [ms^2]	888.0 ± 673.8	1092.5 ± 968.2	1862.3 ± 1357.7	1978.5 ± 1635.7	1440.1 ± 992.3	0.001
HR-RRI [ms^2]	601.0 ± 492.1	954.4 ± 793.1	1571.3 ± 1529.0	1443.5 ± 1544.6	890.5 ± 866.9	0.123

HF — high-band frequency spectrum; LF — low-band frequency spectrum; PSD — **??**
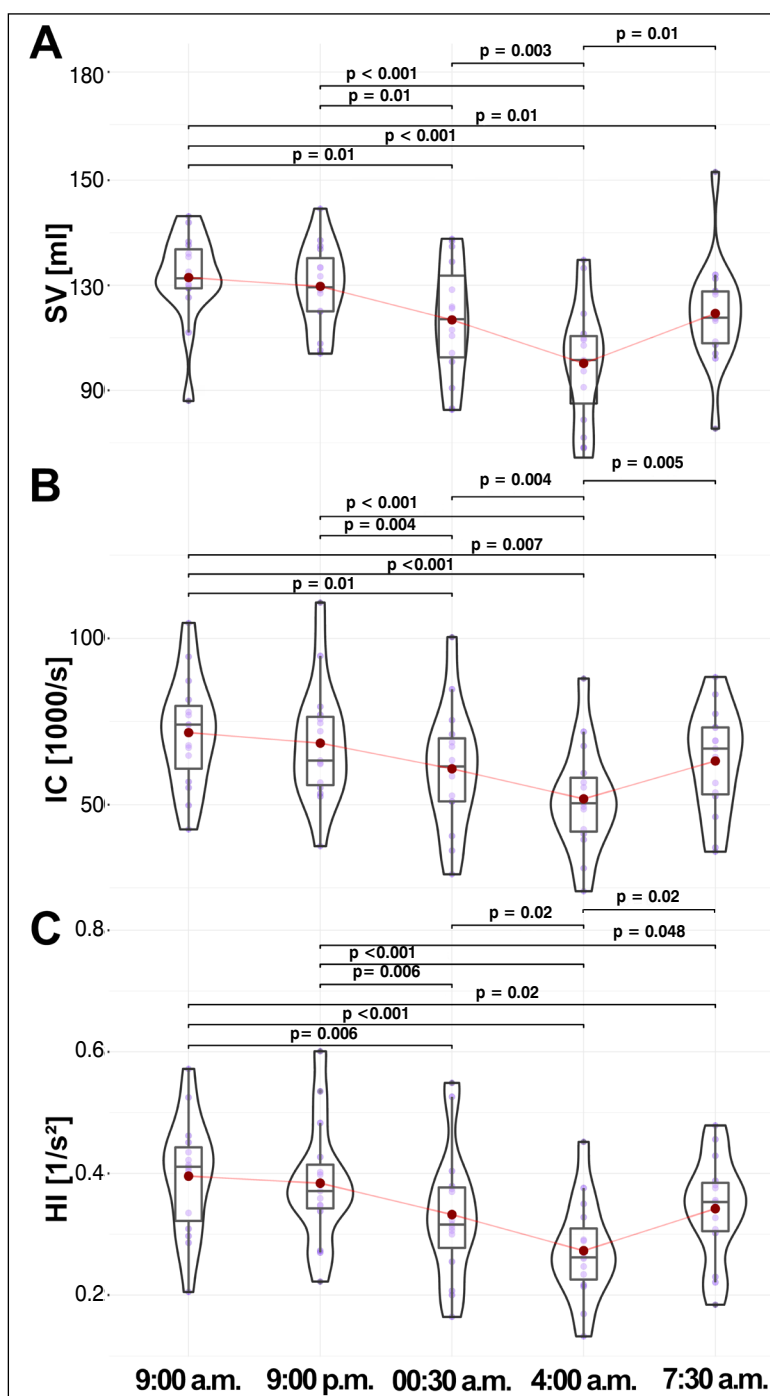
Figure 1. Influence of sleep fragmentation on cardiac contractility parameters. Red dots connected by the red line indicate the mean value, and horizontal black lines inside the box denote the median value. Coloured dots inside graphs denote the results of individual patients. Shapes of violin graphs indicate the distribution of results
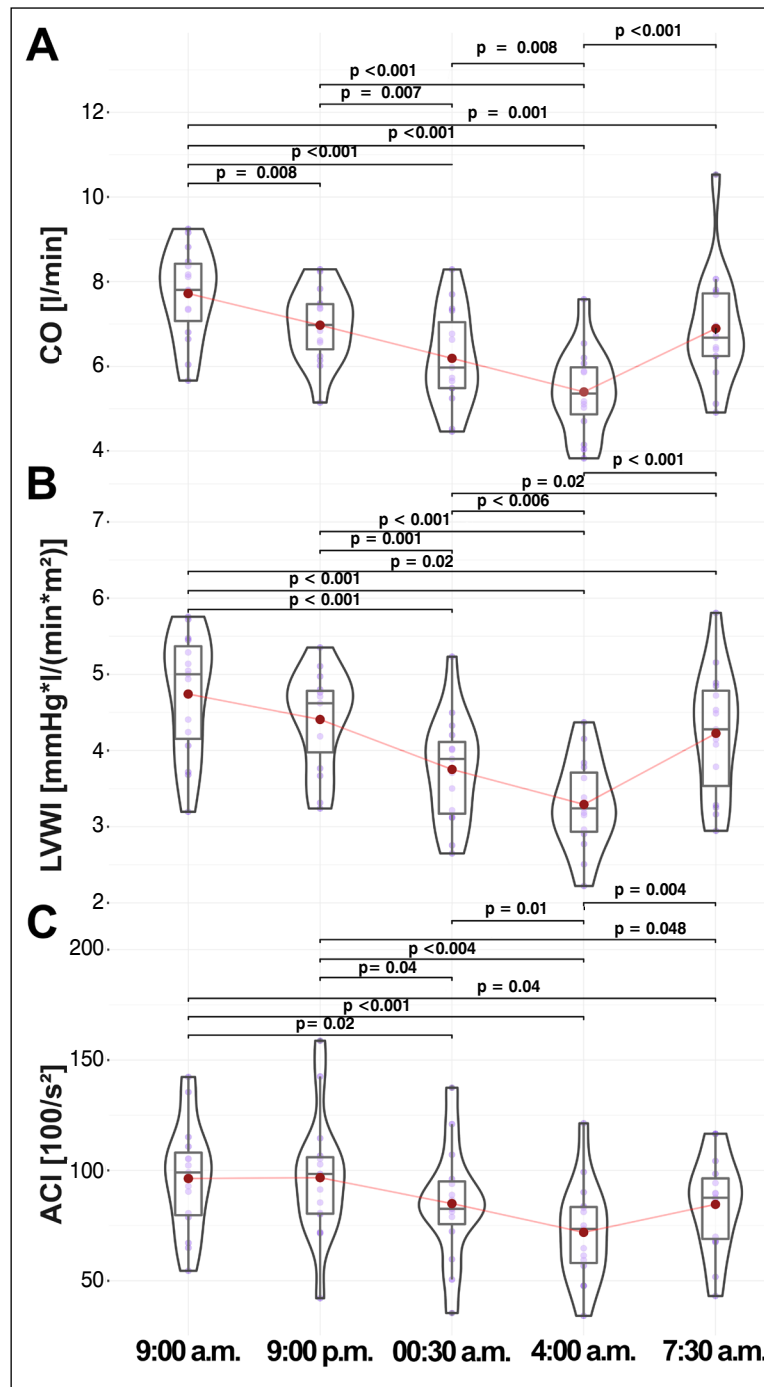
Figure 2. Influence of sleep fragmentation on indexes of left ventricle workload. Red dots connected by the red line indicate the mean value, and horizontal black lines inside the box denote the median value. Coloured dots inside graphs denote the results of individual patients. Shapes of violin graphs indicate the distribution of results.

Sleep fragmentation had a significant influence on indexes related to cardiac contractility: on SV ($p < 0.0001$, $\omega^2_p = 0.23$ (0.03; 0.39), IC ($p < 0.001$, $\omega^2_p = 0.13$ (0.00; 0.27), HI ($p < 0.001$, $\omega^2_p = 0.16$ (0.00; 0.31).

SV decreased from 9:00 p.m. in comparison to 3 and a half hours later (119.7 *vs.* 110.1 mL, $p = 0.01$) and then from 00:30 a.m. to 4:00 p.m. ($p = 0.003$). Then, in comparison to 4:00 a.m. SV increased at 7:30 a.m. (from 97.7 to 112 mL, $p = 0.01$) (Fig. 1). IC and HI have
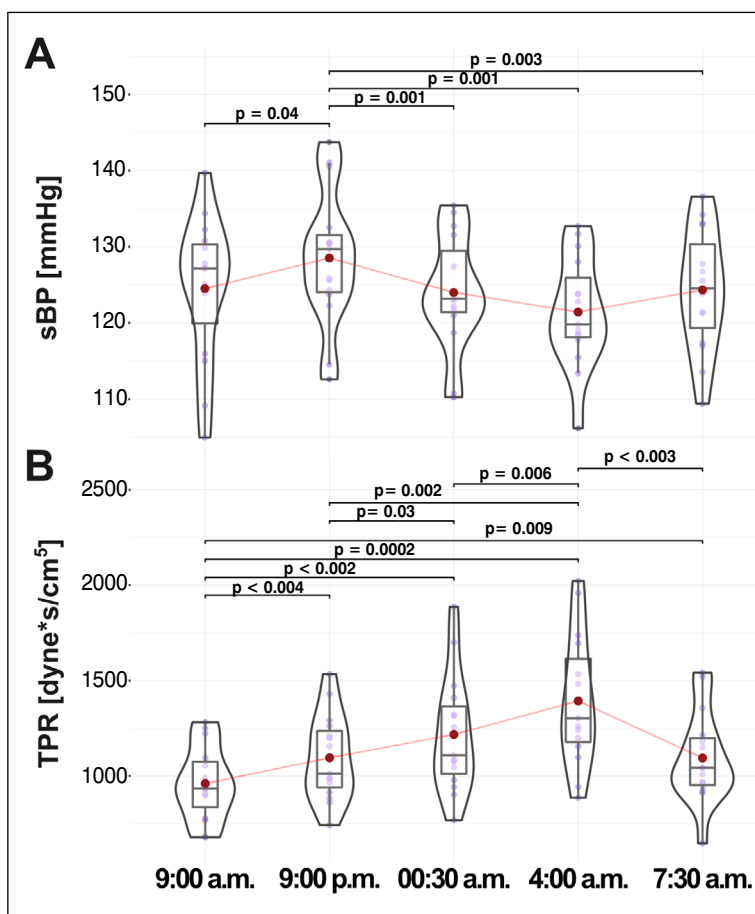
Figure 3. Influence of sleep fragmentation on parameters related to blood pressure regulation. Red dots connected by the red line indicate the mean value, and horizontal black lines inside the box denote the median value. Coloured dots inside graphs denote the results of individual patients. Shapes of violin graphs indicate the distribution of results.

followed a similar pattern of changes to SV in response to sleep fragmentation (Fig. 1, Tab. 1).

Sleep fragmentation had a significant influence on indexes related to workload of the left ventricle: on CO (p < 0.001, WKendall = 0.71 (0.72; 0.88), on LVWI (p < 0.001, ω^2_p = 0.33 (0.11; 0.48) and on ACI (p < 0.001 ω^2_p = 0.11 (0.00; 0.24). CO decreased from 9:00 p.m. to 00:30 a.m. (7 L/min vs. 6.2, p = 0.007), and then decreased as well from 00:30 a.m. to 4:00 a.m. (from 6.2 to 5.4, p = 0.008). Then, CO increased from 4:00 a.m. to 7:30 (5.4 vs. 6.9 L/min, p < 0.0001). LVWI and ACI have followed a similar pattern of changes to CO in response to sleep fragmentation (Fig. 2, Tab. 1).

Sleep fragmentation had a significant influence on parameters related to blood pressure regulation: on sBP (p = 0.001, ω^2_p = 0.06 (0.00; 0.16), and TPR (p < 0.0001, ω^2_p = 0.22 (0.02; 0.37)

SBP decreased from 129 mmHg at 9:00 p.m. to 124 mmHg at 00:30 a.m. (p = 0.001). SBP decreased from 9:00 p.m. in comparison to 4:00 a.m. (from 129 mmHg at 9:00 p.m. to 121 mmHg, p = 0.001). Then,

sBP had a non-significant tendency to increase from 4:00 a.m. to 7:30 a.m., TPR increased from 9:00 p.m. to 00:30 a.m., and then from 00:30 a.m. to 4:00 a.m. Conversely, TPR decreased from 4:00 a.m. to 7:30 a.m. (Fig. 3, Tab. 1).

Sleep fragmentation had a significant influence on chronotropic parameters: on HR (p < 0.001), ω^2_p = 0.23 (0.03; 0.38), PEP (p < 0.001, ω^2_p = 0.11 (0.00; 0.23) and LVET (p < 0.001, ω^2_p = 0.24 (0.04; 0.39). Post-hoc analysis revealed a significant decrease in HR from 9:00 p.m. in comparison to 6 hours later (58.4 vs. 55.6 bpm, p < 0.001 Then, after 4:00 p.m. HR increased at 7:30 a.m. the next day (55.6 vs. 61.7 bpm, p < 0.001). PEP increased from 109 ms at 9:00 p.m. to 119 ms at 4:00 a.m. (p = 0.003). Moreover, PEP increased from 0:30 a.m. to 4:00 a.m. (from 113 to 119 ms, p = 0.009). Then, PEP decreased from 119 ms to 110.5, p = 0.002). LVET increased from 9:00 p.m. to 00:30 a.m. (from 326 ms to 331 ms, p = 0.01). Then, LVET decreased from 4:00 a.m. to 7.30 a.m. (from 330 ms to 322 ms, p = 0.01) (Fig. 4, Tab. 1).
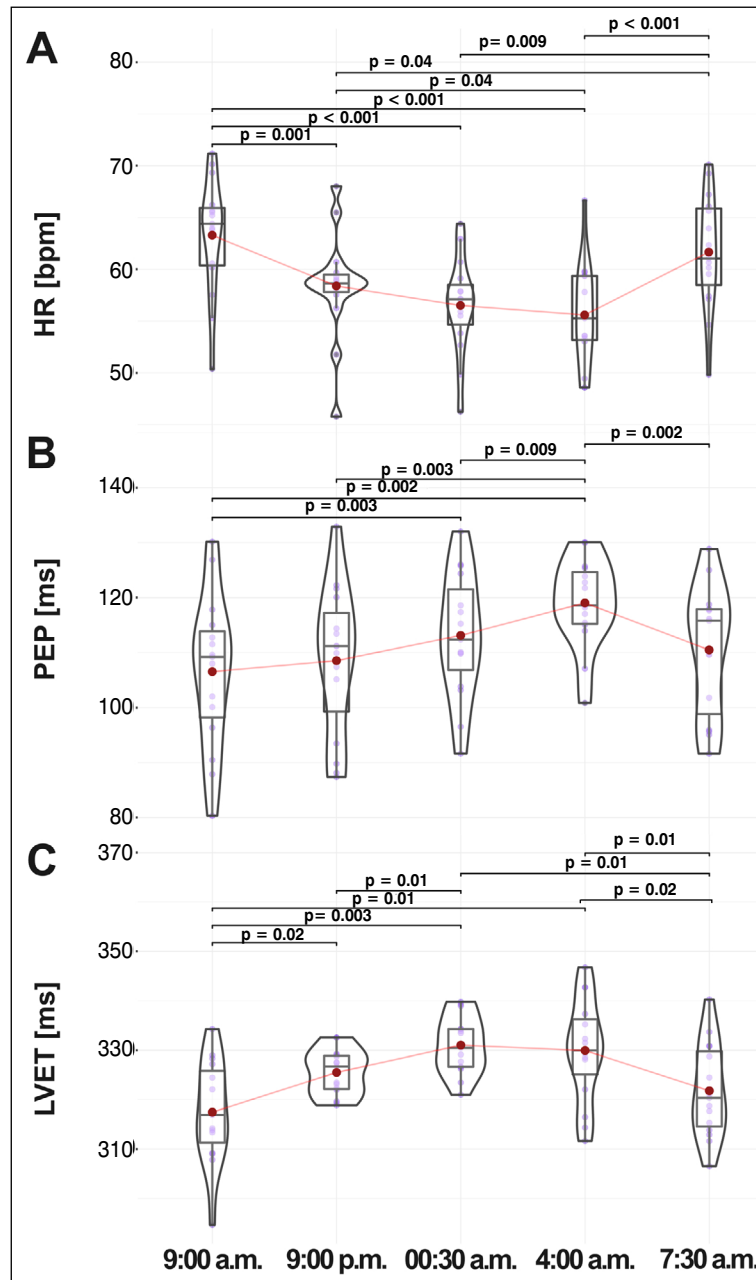
Figure 4. Influence of sleep fragmentation on chronotropic parameters. Red dots connected by the red line indicate the mean value, and horizontal black lines inside the box denote the median value. Coloured dots inside graphs denote the results of individual patients. Shapes of violin graphs indicate the distribution of results

Sleep fragmentation had a significant influence on an indicator of cardiac autonomic regulation: LF-RRI ($p = 0.001$, WKendall = 0.69 (0.68; 0.90). LF-RRI increased from 1093 at 9:00 p.m. to 1862 at 00:30 a.m. ($p = 0.03$). Moreover, LF-RRI increased from 9:00 p.m. in comparison to 4:00 a.m. ($p = 0.02$). LF-RRI was significantly higher at 7.30 a.m. the next day in comparison to 9:00 a.m. before sleep fragmentation (1440 vs. 888, $p = 0.03$) (Fig. 5, Tab. 2). However, the influence on an indicator of parasympathetic cardiac regulation (HF-RRI) was not statistically significant ($p > 0.05$) (Tab. 2).

Discussion

The present study's major finding is that during sleep fragmentation, healthy men experience changes in haemodynamic parameters, heart contractility and autonomic nervous system function; the most import-
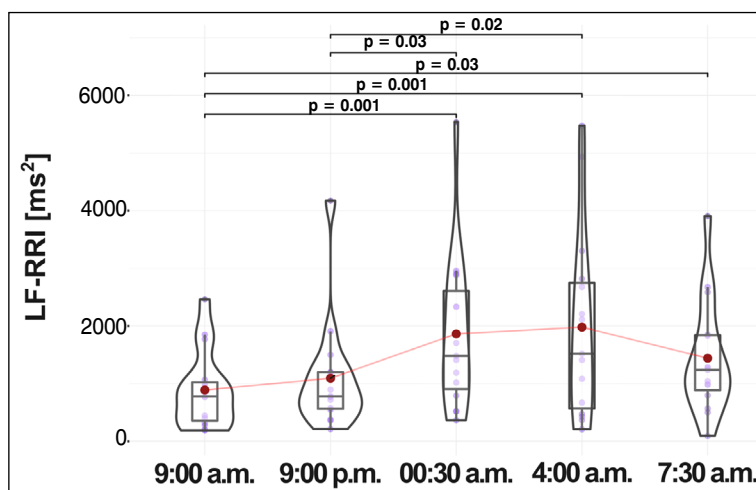
Figure 5. Influence of sleep fragmentation on an indicator of cardiac autonomic regulation. Red dots connected by the red line indicate the mean value, horizontal black line inside the box denotes the median value. Coloured dots inside graphs denote the results of individual patients. Shapes of violin graphs indicate the distribution of results.

ant changes were observed at 4:00 a.m. compared to baseline. There were significant changes in systolic blood pressure, however with a small effect size relative to changes in the other examined parameters. At 4:00 a.m. compared to baseline was observed a decrease in volumetric parameters (SV, CO, TPR), and a decrease in myocardial contractility, i.e. HI, ACI, IC. Observed changes resulted in an increase in the left ventricular ejection time (LVET) and pre-ejection period (PEP). In the current literature, changes in cardiac function during sleep fragmentation or even acute sleep deprivation are less well-defined [21]. The authors' previous study has shown that sleep fragmentation affects haemodynamics, notably stroke index more than sleep deprivation [22].

During sleep fragmentation, an increase in LF-RRI was noted. However, changes in HF-RRI were not statistically significant. HF-RRI is an indicator of parasympathetic activity [23]. Since LF may be affected both by sympathetic and parasympathetic activation [24, 25], it could be concluded that changes in LF-RRI in the above study were caused by the influence of the sympathetic branch of ANS in a greater manner than other factors. This is confirmed by the results of studies showing that the markers of sympathetic nervous system activity, i.e. adrenaline, noradrenaline, or cortisol, reach the highest values in the morning, which correlates with an increased incidence of ischaemic cardiac events at this time of the day. Somers et al. have shown that sympathetic nervous system activity assessed by the microneurography method is higher during the rapid eye movements (REM) phase than during all NREM stages and significantly exceeds the level of sympathetic nervous system activity during wakefulness [25]. Since

the amount of REM sleep is dominant in the second part of the night immediately before awakening this is a postulated relationship between sympathetic nervous system activation of REM sleep and increased incidence of cardiovascular events in the morning compared to other times of the day. Sleep fragmentation is probably related more to the shortening of NREM sleep (than REM sleep). Thus, during the night, higher levels of sympathetic activity are stabilized, resulting in the fixation of this pattern. Sleep deprivation does not promote an increase in sympathetic activity, typical for REM sleep.

Previous studies show that disturbances in the sleep/wake cycle (i.e. sleep fragmentation, shift work) cause misalignment of the endogenous rhythm and are associated with an increased risk of developing cardiovascular or metabolic disorders [26]. Boggild and Knutsson in their meta-analysis show that shift workers had a 40% increased risk of cardiovascular disease compared with daytime workers [27]. Several other causes of sleep fragmentation (i.e. pain, noise, bruxism) have been shown to produce sympathetic overactivity during sleep. Chouchou et al. noticed a positive relationship between sympathetic sleep fragmentation and 24h BP in a large population of elderly volunteers. Other authors suggest that using autonomic parameters to assess sleep fragmentation could add clinical information about hypertension risk [28].

The present study has several strengths. First, to the best of the authors' knowledge, this is the first study evaluating the effect of acute, induced sleep fragmentation in standardized conditions on autonomic cardiovascular regulation. What is important, the results of this study have proved that variability of haemody-

namic and autonomic parameters depends on sleep fragmentation timetables. The strengths of this study should be weighed against some limitations. First, it was a relatively small study population. However, conducting chronobiology clinical research presents challenges because of the specificity of sleep research and its high cost. The other was the lack of an objective sleep measure (e.g. polysomnography) during sleep fragmentation.

Conclusions

In conclusion, these findings have a few implications. Observed cardiac function changes, especially noticeable at 4:00 a.m. testify to the high variability of the examined parameters, especially in the morning hours. Conditions of chronic sleep fragmentation (e.g. shift work, uniformed services, clinicians), might lead to disturbance in the autonomic nervous system, which in turn may result in an increased frequency of cardiovascular events in the morning hours than at other times of the day.

Conflicts of interests: *None.*

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