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The impact of total sleep deprivation upon supine and head up tilt hemodynamics using non-linear analysis in firefighters

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The impact of total sleep deprivation upon hemodynamic function

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Abstract

Purpose The impact of 31 hours of total sleep deprivation (TSD) on cardiovascular autonomic modulation was evaluated in 46 volunteers all professional fire brigade units officers (all men, mean age=32.11±6.4).

Methods Hemodynamic examination was obtained at baseline and after 31 hours of Total Sleep Deprivation (TSD). Each measurement period included supine and head-up tilt (HUT) test response. Continuous beat-to-beat systolic blood pressure (sBP), diastolic blood pressure (dBP) and mean blood pressure (mBP), heart rate (HR), stroke volume (SV), left ventricular ejection time (LVET) and cardiac output (CO) were calculated in rest supine position and in response to HUT. Nonlinear analyses were conducted using Permutation Entropy (PE), Amplitude Aware Permutation Entropy (AAPE) and Fractal Dimension (FD).

Results Supine increase of HR and decrease in RRI, LVET and entropy of LVET were observed after 31-h of TSD. Increase in entropy of mBP was indicated by AAPE and PE methods. Response to HUT, values of spectral analysis of blood pressure (normalized units of high frequency of sBP and dBP) was altered. Permutation entropy of mBP in response to HUT were significantly changed after 31-h of TSD.

Conclusions TSD alters autonomic nervous system modulation of cardiac and vascular functioning while supine and in response to orthostatic stress. TSD resulted in changes in cardiac and both spectral and two methods of analysis of entropy of blood pressure when supine. Values of spectral analysis of blood pressure and permutation entropy of mean blood pressure in response to HUT were significantly changed after 31 h of TSD.
Key words sleep restriction; permutation entropy; autonomic nervous system; complexity

Abbreviations

AAPE Amplitude Aware Permutation Entropy

dBP Diastolic Blood Pressure

FD Fractal Dimension

HFnu@ normalized High Frequency spectral component of @

HR Heart Rate

HRV Heart Rate Variability

HUT Head Up Tilt

LFnu@ normalized Low Frequency spectral component of @

LVET Left Ventricular Ejection Time

mBP Mean Blood Pressure

PE Permutation Entropy

RRI Heart Interval

sBP Systolic Blood Pressure

SV Stroke Volume
TSD Total Sleep Deprivation
Total sleep deprivation can induce changes in supine heart rate (HR) and blood pressure (BP) dynamics (Zhong et al. 2005). Initial increase in low frequency and decrease in high frequency spectral components of heart rate variability (HRV) and later decrease of overall autonomic nervous system cardiac outflow has been observed in response to Total Sleep Deprivation (TSD) (Chua et al. 2012). Sleep deprivation is more prevalent in modern societies potentially contributing to cardiovascular and metabolic disorders (Tobaldini et al. 2017). Potential part of pathomechanism might lead in alternation of autonomic nervous system (ANS) by TSD (Tobaldini et al. 2017). TSD is the most commonly used model of sleep deprivation experienced as part of shiftwork (e.g. truck drivers, medical professions, etc.) (Reynolds, Banks 2010). Therefore, many researchers have focused on examination of impact of the TSD on ANS function. For example, Zhong et al. (Zhong et al. 2005) investigated cognitive and autonomic function at several time points during TSD. A gradual increase in the LF component of HRV execution of cognitive tasks during TSD has been observed (Zhong et al. 2005). Nevertheless, to our knowledge, only one paper describes differences in the response to HUT during TSD (Tobaldini et al. 2013). However, Tobaldini et al. used spectral analyses of heart rate (HRV) and blood pressure variability (BPV) as indicators of ANS functioning. In the present study, we have decided to use wider range of methods of signal analysis. There are various commonly known mathematical method in time - domain and frequency - domain applied for HRV and blood pressure variability (BPV) analysis in order to investigation the complexity and nonlinearity in cardiovascular signals (Zhong et al. 2005, Tobaldini et al. 2013). Recently various nonlinear algorithms have been developed (entropy, recurrence methods, fractal dimension (FD), Lapunov exponents) and ect to reveal chaotic or irregular
dynamics of hemodynamic parameters. Entropy has become widely applied in analysis of biosignals since 1991, when Pincus proposed the Approximate Entropy as a measure of cardiovascular signal complexity (Pincus, Huang 1992, Pincus 1995). Nowadays have been introduced many advanced algorithms for calculating entropy. There is also a large group of investigators aiming connect the complexity measures of physiological signals to autonomic nervous system (Barbieri et al. 2017). Following the broad cardiovascular studies about application of entropy in ECG and blood pressure analysis we also applied this measure in our investigations. As a complexity measure of sBP, dBP, mBP, HR, SV, LVET and CO we choose permutation entropy (PE) and Amplitude Aware Permutation Entropy (AAPE) (Brandt and Pompe 2002, Azami and Escudero 2016). Permutation entropy (PE) has been shown to be effective in classification of fetal state classification (Frank et al. 2006) and left ventricular ejection time in response to HUT was evaluated using the fractional shortening method (Mizumaki et al. 1995). It was suggested (Ravelo-García et al. 2015) that permutation entropy of HRV signal could be useful in electrocardiogram-based sleep breathing pause detection. Other researchers (Graff et al. 2015) have found permutation entropy clinically useful in the identification of patients with cardiodepressive vasovagal syncope. A decrease in PE in response to HUT in 17 healthy participants was reported (Cysarz et al. 2013). In addition, application of three methods of entropy evaluation indicated a decrease of complexity caused by the table inclination during HUT (Porta et al. 2007). The significant changes in PE calculated for biosignals recorded during HUT test performed for the patients suffered for VVS were described previously (Buszko et al. 2017). Inspired by studies mentioned above, we would like to examine the influence of 31 hours of TSD on hemodynamic parameters, their values of spectral analysis and 3 non-linear measures in supine and in response to HUT. Professional firefighters were chosen as a sample due to the high occurrence of healthy, young
men. According to our knowledge, this is the first study to use those methods in examination of the TSD influence.
Materials and methods

Study protocol

The examination was performed in the chronobiology laboratory while maintaining constant conditions (constant routine, temperature 22°C, humidity 60%, light <10 lx). Light intensity control is crucial due to the known differences in HRV between dim and bright light conditions during sleep deprivation (Yokoi et al. 2006). Subjects arrived at the laboratory at 07:30 A.M. after their typical sleep at home the night before (total sleep time, TST=421.2±68.2 min). Subjects ate the same meals at the same time of the day (8:00, 12:00, 15:00, 19:30). Water (100 ml) was administered at hourly intervals during the protocol. The subjects were cared for by trained personnel. Reading, writing, talking, and playing games were allowed during the experiment. Additionally, the device Actigraph GT3X (Actigraph, Pensacola, FL, USA) was used during the experiment to monitor subjects' sleep deprivation and motor activity (Tweedy and Trost 2005; Tryon 2004, Santos-Lozano et al. 2013). After a normal night of sleep (the rest state) subjects underwent training in test procedures. Following arriving in the laboratory at 7:30 hours on Day 2 (Day 1 = normal sleep), volunteers began regular hemodynamic testing throughout the sleep deprivation period. The next measurement where set on 4 p.m. the next day (Day 3).

Study group

Sixty volunteers took part in the study— all were active male fire brigade officers working in fire brigade units in the Kujawsko-Pomorskie Voivodeship, Poland. N=14 participants were excluded due to technical problems with data acquisition. Finally, data from 46 participants
were taken into analysis. The study was approved by the Ethics Committee, Ludwik Rydygier Memorial Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Torun. The subjects met the following criteria for enrollment into the study group: (a) active service as a fire brigade officer, (b) positively evaluated health status following a standard comprehensive physical examination. In addition to giving their voluntary consent to participation in the study, the main enrollment criteria included sex (males only were chosen to exclude potential role of menstrual cycle on the outcome), no co-morbidity, no reported low sleep quality (Pittsburgh Sleep Quality Index <5 (Buysse et al. 1989). Pre-test of the subjects health state assessment included: the basic neurological, clinical examination, evaluation of the autonomic nervous system using the Autonomic Symptom Profile (Suarez et al. 1999). Exclusion criteria consisted of extremely morning/evening chronotype, any caffeine or alcohol taken during the study or within 12 hours before the test, drugs dependence, participation in sports at competitive level, receiving any medication/supplements during the study and potential disorders of the cardiovascular observed during the test experiment.

Baseline values of demographic and physiological parameters of examined group are described in Table 2.

**Table 2. Global characteristic of examined group**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Median</th>
<th>Quartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.11</td>
<td>6.41</td>
<td>31.5</td>
<td>5</td>
</tr>
<tr>
<td>Height [m]</td>
<td>1.8</td>
<td>0.06</td>
<td>1.80</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>84.11</td>
<td>12.04</td>
<td>82.00</td>
<td>19.00</td>
</tr>
<tr>
<td>BSA</td>
<td>2.03</td>
<td>0.15</td>
<td>2.04</td>
<td>0.24</td>
</tr>
<tr>
<td>BMI</td>
<td>26.01</td>
<td>3.56</td>
<td>25.04</td>
<td>4.97</td>
</tr>
<tr>
<td>HR</td>
<td>60.52</td>
<td>8.57</td>
<td>60.79</td>
<td>10.93</td>
</tr>
<tr>
<td>sBP</td>
<td>126.62</td>
<td>14.96</td>
<td>124.01</td>
<td>20.85</td>
</tr>
<tr>
<td>dBP</td>
<td>79.29</td>
<td>10.6</td>
<td>77.53</td>
<td>16.60</td>
</tr>
</tbody>
</table>
The mean age of participants was 32.11±6.4. All of 46 participants completed the whole TSD protocol, no adverse events were reported.

**Hemodynamic parameters measurement**

All data were collected noninvasively by Task Force Monitor (CNS Systems, Gratz, Austria). Finger blood pressure was measured by the vascular unloading technique (Fortin et al. 1998), corrected automatically to the oscillometric measured BP on the contralateral arm. Continuous beat-to-beat systolic blood pressure (sBP), diastolic blood pressure (dBP) and mean blood pressure (mBP) values were automatically evaluated. The heart rate (HR) was derived from electrocardiogram (ECG) (sampling frequency: 1000 Hz). Impedance cardiography (ICG) method was used to calculate the stroke volume (SV), and left ventricular ejection time (LVET; the time interval from the opening to the closing of the aortic valve [mechanical systole]). Moreover, based on HR and SV, cardiac output (CO) was calculated. In brief, blood pressure, heart rate, SV, CO and LVET are indicators of cardiovascular system functioning, which potentially might be affected by TSD.

Parameters were recorded continuously in a supine position for 15 minutes after stabilization of the signals. Then, passive head up tilt test (HUT) was performed at 70° angle of inclination, for 6 minutes. Duration of HUT was chosen based on previous studies (Estévez et al. 2016). As total hemoglobin concentration in muscles depend on angle of inclination, all HUT tests were applied with the same parameters (Çotuk et al. 2016). 70° angle of inclination was chosen according to Newcastle protocol (Kenny et al. 2000). A tilt table with a foot support and
fastening straps at the knee, hip and chest levels was used to change passively the body position. Response to HUT in each time point was calculated based on difference between mean value from rest in supine position and mean value from tilt test.

**Data preparation and analysis**

Beat-to-beat data were filtered using Grubbs’s test for outliers’ elimination. The software implemented in TFM assess the heart rate and blood pressure variability in real-time through implementation of "Adaptive Autoregressive Parameters" (AAR) (Fortin et al. 1998). Adaptive parameter identification which obtains weighted values of a sliding exponential or whale formed window determine the time-variant autoregressive coefficients. Adaptive autoregressive coefficients derived from hemodynamic parameter are used to calculate the time-varying power spectrum (Fortin et al. 1998). Autonomic parameters were calculated using AAR from beat-to-beat RRI using spectral method analysis of the heart rate variability (HRV). LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz) of the RRI of an ECG complex and sBP (systolic BP) and dBP (diastolic BP) variability were calculated using autoregressive power spectra method and expressed in normalized units (Fortin et al. 1998; Camm 1996). The HF (high-frequency) band of the power spectra of RRI is thought to reflect the activity of parasympathetic branch of ANS, whereas the LF (low-frequency) component of RRI reflects both the sympathetic and parasympathetic output. The LF/HF ratio power is used as an indicator of sympathovagal balance (Pagani et al. 1986). Taking into account limitations in quantifying ANS activity by frequency methods (Karemaker 1997), autonomic modulation of the sinoatrial node and vasomotion could be described by LF diastolic blood pressure to HF(RRI) (Pagani et al. 1986; Camm et al. 1996). Normalized units (LFnu and HFnu) are reported and analyzed.
Permutation Entropy (PE), Amplitude Aware Permutation Entropy (AAPE) and Fractal Dimension (FD) - theoretical background

The presented analysis of entropy was based on Permutation Entropy (PE) and Amplitude Aware Permutation Entropy (AAPE) introduced by Azami and Escudero 2016. Originally Permutation Entropy (PE) was proposed by Bandt and Pompe 2002 as a complexity measure for time series. The main advantages of PE were simplicity, robustness, invariance with respect to nonlinear monotonous transformations and extremely fast calculation. Premutation Entropy belongs to a wide class of ordinal and symbolic methods. It means that the analysis is not directly based on the values of the analyzed time series but on the relation between them. The detailed description of the algorithm for PE and discussion about its properties is available in (Bandt and Pompe 2002, Li et al. 2018). Here, we briefly describe the main idea of PE calculation.

Given a time series with length $N$:

\[
\{x_i\}_{i=1}^N = \{x_1, x_2, ..., x_N\}. \tag{1}
\]

Embedding the signal $x_i$ in a $d$ - dimensional space with delay time $l$ we obtain a set of reconstruction vectors:

\[
X_t^{d,l} = \{x_t, x_{t+1}, ..., x_{t+(d-2)l}, x_{t+(d-1)l}\}, \tag{2}
\]

where $t = 0, 1, 2 ..., N - (d - 1)$. Each $X_t^{d,l}$ is arranged in an increasing order as follows:

\[
\{x_{l+(j_1-1)l} \leq x_{l+(j_2-1)l} \leq \ldots \leq x_{l+(j_{d-1}-1)l} \leq x_{l+(j_d-1)l}\} \tag{3}
\]

where $j = 1, ..., d$ is the index of the element in the reconstruction vector. Such process, named symbolization process, allows to obtain ordinal pattern $\phi_t = \{r_0, r_1, ..., r_{d-1}\}$ that describes each
vector $X_t^{d,l}$. The symbolization process yields $d!$ potential ordinal patterns termed “motifs”.

The relative frequency of occurrence permutation pattern $\pi_k$ is as follows:

$$p(\pi_k) = \frac{\sum_{i=1}^{N-d+1} \delta(\pi_k, \varphi_i)}{N-d+1},$$

(4)

where $\delta(\pi_k, \varphi_i)$ is the Kronecker delta function ($\delta(\pi_k, \varphi_i)$ equal 1 when the ordinal pattern $\pi_k$ corresponds to the permutation pattern $\varphi_i$ and 0 in another cases.

Permutation entropy (PE) is calculated as:

$$PE(X, d, l) = - \sum_{i=1}^{i=d!} p(\pi_i) \cdot \ln(p(\pi_i)).$$

(5)

Generally, the higher value of PE is obtained, the more complex dynamical system is described by the analyzed time series. Maximal value of PE reaches $\ln(d!)$ and it occurs when all patterns are equally probable. It indicates that the signal is completely random. PE is minimal for strictly monotonic signals ($PE = 0$). The normalized PE can be calculated using the formula:

$$PE(X, d, l) = - \frac{1}{\ln(d!)} \sum_{i=1}^{i=d!} p(\pi_i) \cdot \ln(p(\pi_i)).$$

(6)

To obtain reliable PE embedding dimension should be high enough (from the practical point of view it is recommended choosing $d$ between 3 and 7 but such to fulfill $d! << N$). In our investigation $d$ was set on 4.

Permutation Entropy (PE) is very useful and friendly method for calculating entropy because it is computationally fast, has minimal set of parameters and does not require a long times series, although it is also suitable for big data sets. Despite the list of advantages is wide, the estimation of PE according to the procedure described above has two key disadvantages. Firstly, when only ordinal structure of time series is to be considered, some information might be missed. The same permutation pattern could have vectors with totally different amplitudes and average of its element’s values. Secondly, differences between amplitude values might not
lead to different motifs (Azami and Escudero 2016). To came abovementioned drawbacks over
Azami and Escudero proposed modified version of PE calculation. To address the mentioned
problems they proposed corrections in calculating the relative frequency $p(\pi_k)$ adding
contributions depending on average absolute amplitude (AA) and relative amplitudes (RA) (Li
et al. 2018). The second issue was eliminated by discrimination between strictly
ascending/descending and only ascending/descending sequences (Azami and Escudero 2016).
They sum up all contributions coming from motifs representing the same state and divide them by the number of potential permutation of those states.

The formulas for (AA) and (RA) for vector $X^{d,l}_t$ are:

$$AA_t = \frac{A}{d} \sum_{i=1}^{d} |x_{t+(i-1)d}|,$$  \hspace{1cm} (7)

and

$$RR_t = \frac{1-A}{d-1} \sum_{i=2}^{d} |x_{t+(i-1)d} - x_{t+(i-2)d}|,$$  \hspace{1cm} (8)

The formula for relative frequency calculation in AAPE method is:

$$p^*(\pi_k) = \frac{\sum_{i=1}^{N-d+1} \delta(\pi_k, \phi_{i}) \cdot (AA_{A} + (1-A) \cdot RA_{t})}{\sum_{i=1}^{N-d+1} AA_{A} + (1-A) \cdot RA_{t}},$$  \hspace{1cm} (9)

where $A \in [0,1]$. Depending on the study one can emphasize either the changes of amplitude values or average of amplitude values. Typically $A = 0.5$ is recommended.

The formula for AAPE calculation is as follow:

$$AAPE(X, d, l, A) = - \sum_{i=1}^{l} p^*(\pi_i) \cdot \ln(p^*(\pi_i)).$$  \hspace{1cm} (10)

The normalized AAPE is:

$$AAPE(X, d, l, A) = - \frac{1}{\ln l} \sum_{i=1}^{l} p^*(\pi_i) \cdot \ln(p^*(\pi_i)).$$

The flow chart of the AAPE method is presented on the figure 1.
Start

Input the time series: \( \{x_i\}_{i=1}^N = \{x_1, x_2, ..., x_N\} \)

Input the parameters: \( d, l, A \)

Create the reconstruction vectors:
\[
X_{t}^{d,l} = \{x_t, x_{t+1}, ..., x_{t+(d-2)l}, x_{t+(d-1)l}\}
\]

Determine the permutation patterns \( \pi_k \), where \( k = 1, ..., N - d + 1 \)

Is \( \pi_k \) strictly ascending or descending?

Yes

\[
p^{**}(\pi_k) = \frac{\sum_{l=1}^{N-d+1} \delta(\pi_k, \pi_l)/w}{N-d+1}
\]

No

\[
p^{*}(\pi_k) = \frac{\sum_{l=1}^{N-d+1} \delta(\pi_k, \varphi_l)}{N-d+1}
\]

\[
p(\pi_k) = p^{*}(\pi_k) + p^{**}(\pi_k)
\]

\[
APE(X, d, l, A) = -\sum_{i=1}^{l/d} p^{*}(\pi_i) \cdot \ln \left( p^{*}(\pi_i) \right)
\]
As the third non-linear method for analyzing the data we have chosen fractal dimension (FD). Fractal Dimension is commonly known nonlinear parameter applied for analyzing biosignals especially for EEG analysis (Khoa et al. 2012). There are some algorithms used for FD assessment like Higuchi algorithm (Higuchi 1988), Kantz (Katz 1988) and Petrosian algorithm (Petrosian 1995), Burlaga and Klein (Burlaga and Klein 1986) and etc. We calculated FD for measured signals using Higuchi algorithm (Higuchi 1988) because the calculations of
FD are performed in the time domain. The algorithm was explained in detail in (Higuchi 1988).

Here we briefly describe the main idea of the numerical calculations.

For a time series (1) one construct a new time series according to the formula:

\[ X^m_k : X(m) \text{, } X(m + k) \text{, } X(m + 2k) \text{, } \ldots \text{, } X \left( m + \right. \int \left( \frac{(N-m)}{k} \right) \cdot k \left. \right), \]  

(12)

where \( m = 1, 2, \ldots, k \) is initial time and \( k \) is interval time, \( \int \) means the integer part of \( \left( \frac{(N-m)}{k} \right) \). The fractal dimension (FD) is connected with a measure of length \( L(k) \) of each curve \( X^m_k \) calculated using the formula:

\[ L(k) = \frac{\sum_{m=1}^{k} L_m(k)}{k}, \]  

(13)

where

\[ L_m(k) = \frac{1}{k} \left[ \left( \sum_{i=1}^{\int \left( \frac{(N-m)}{k} \right)} |X(m + i \cdot k) - X(m + (i - 1) \cdot k)| \right) \times \frac{N-1}{\int \left( \frac{N-m}{k} \right)} \right]. \]  

(14)

The \( L_m(k) \) is not an Euclidean measure of curve’s length but it is the normalized sum of absolute differences between pairs of points with distance \( k \). The fractal dimension (DF) is related to \( L(k) \) in the following way:

\[ L(k) \sim k^{-DF}. \]  

(15)

The least squares linear best fitting procedure is applied for determining DF. In graphical interpretation on doubly logarithmic scale for \( L(k) \) plotted against \( k \) the slope of the best
fitted straight line for the data is equal $-DF$. The flow chart for DF calculation is presented on figure 2.
Figure 2. The flow chart for calculating fractal dimension (DF).


In order to compare the changes of FD and entropy during experimental procedure the mentioned measures were evaluated for exactly the same recorded signals.

The MATLAB code of Amplitude Aware Permutation Entropy (AAPE) calculation is available at https://datashare.is.ed.ac.uk/handle/10283/1918 and it was described in detail previously (Azami and Escudero 2016). The method of calculating fractal dimension of a time series directly in the time domain is available at https://file.scirp.org/pdf/WSN20100100010_27519619.pdf. To compare signal FD and entropy changes during experimental procedure FD were evaluated for exactly the same signals as AAPE.

Numerical and statistical analysis

Permutation Entropy (PE) and Amplitude Aware Permutation Entropy (AAPE) were calculated for raw beat to beat data of RRI, HR, dBS, sBP, mBP, LVET, SV and CO time series. Data were inspected for presence of NaN (Not a Number generated by TFM application in case the program could not properly establish numerical value of the parameter). Time series with more than 4 consecutive NaN’s were rejected. For three or less NaN’s spline function was used to interpolate missing values. Each signal was divided, according to the time protocol, into two epochs, namely supine rest and HUT. During the HUT test the patient is
tilted in short time (5s). The signals recorded in such transient time are too short for preforming the numerical analyses described above. Therefore the transients phases of the test were not considered. According to authors (Azami and Escudero 2016) recommendation order of AAPE ($m$) was set to 4 (however calculation for all orders between 3 and 7 were conducted) and the rest of input parameters reminded default values ($l = 1, A = 0.5$). Signals accepted for analysis have maximal possible length to fulfill $d! \ll N$.

Nonlinear properties of the time series such as signal irregularity could also be assessed by fractal dimension (FD). FD estimation was based on Higuchi algorithm (Al-Nuaimi, et al. 2017). The calculations of entropy and fractal dimension were performed with Matlab R2017a. All statistical analyses were conducted using STATISTICA v.13.1. (StatSoft, Inc. 2014). Assumption of distribution normality was tested using Shapiro-Wilk W test and by histograms investigation. If normality assumption was met, repeated measured ANOVA was used to analyze differences of examined parameters between baseline and 31-h TSD. If not, Wilcoxon signed-rank test was used. Violin graphs were created with ggstatsplot library (Patil and Powell, 2018). Red dots connected by red line indicates mean value, horizontal black line inside the box denotes median value. Green dots before and orange dots after connected by dashed lines denotes results of individual patients. Shape of violin graph indicates distribution of results.

The effect size for ANOVA and Wilcoxon signed-rank tests were calculated (Field 2009).

The significance level was set at $\alpha =0.05$. 


Results

Figure 3 shows sample raw signal from baseline, figure 4 shows sample signal after TSD. Red dashed vertical line indicates point in time when HUT test starts.

Figure 3. Sample raw signal during baseline
Figure 4. Sample raw signal after 31-h of TSD

Significant increase of HR and decrease of RRI were observed in the 31-h of TSD comparing to the baseline, $F(1, 45) = 7.01$, $p = 0.01$, $\omega^2 = 0.0005$ and $z = 2.29$, $p = 0.02$, $r = 0.24$, respectively (Table 3).
Significant decrease of LVET was observed in the 31-h of TSD comparing to the baseline, F(1, 45) = 19.41, p = 0.00007, r = 0.41.

Statistically significant increase of AAPE(mBP) and PE(mBP) entropy were observed in the 31-h of TSD comparing to the baseline, F (1, 45) = 5.7, p = 0.02, ω² = 0.0002 and F(1, 45) = 6.2, p = 0.02, ω² = 0.0002, respectively. Statistically significant differences between baseline and 31-h TSD in parameters measured in supine are shown of Figure 5.

There was no statistically significant differences between baseline and the following time points of TSD in the rest of parameters (p > 0.05).
Figure 5. Differences in baseline vs after 31-h TSD in supine. Red dots connected by red line indicates mean value, horizontal black line inside the box denotes median value. Green
dots during baseline and orange dots after 31 hours of total sleep deprivation connected by dashed lines denotes results of individual subjects. Shape of violin graph indicates distribution of values.

**Table 3.** Physiological parameters during supine. Mean ± SE values are provided in the baseline. P value is result of repeated measured ANOVA or Wilcoxon signed-rank test

<table>
<thead>
<tr>
<th></th>
<th>Baseline Mean±SE</th>
<th>31- h TSD</th>
<th>Δ</th>
<th>CI 95%</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRI</td>
<td>1048.83±21.02</td>
<td>45.58</td>
<td>9.49</td>
<td>81.67</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>58.49±1.09</td>
<td>-2.86</td>
<td>-5.04</td>
<td>-0.68</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>sBP</td>
<td>125.84±1.95</td>
<td>-3.22</td>
<td>-7.55</td>
<td>1.1</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>dBP</td>
<td>80.84±1.51</td>
<td>0.34</td>
<td>-2.47</td>
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<tr>
<td>LVET</td>
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<td>8.92</td>
<td>4.84</td>
<td>13</td>
<td>&lt;0.0001</td>
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<tr>
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<tr>
<td>HFnu-RRI</td>
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<tr>
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<tr>
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<tr>
<td>FD(sBP)</td>
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<td>0</td>
<td>0.03</td>
<td>0.04</td>
<td>0.82</td>
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<tr>
<td>FD(dBP)</td>
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<td>-0.02</td>
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<tr>
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<tr>
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<td>0</td>
<td>0.05</td>
<td>0.07</td>
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<tr>
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<td>0.01</td>
<td>0.82</td>
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<tr>
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<td>-0.07</td>
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<td>PE(SV)</td>
<td>PE(CO)</td>
<td>PE(LVET)</td>
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<td>---------------</td>
<td>-------------</td>
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</tr>
<tr>
<td>Value (±SE)</td>
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<td>2.91 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>3.09 ± 0.01</td>
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</tr>
<tr>
<td>Δ (CI)</td>
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<td>-0.07 -0.14</td>
<td>-0.01 -0.02</td>
<td>-0.01 -0.05</td>
<td>0 -0.02</td>
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<td>0.05</td>
<td>0.02</td>
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<tr>
<td>AAPE(mBP)</td>
<td>2.68 ± 0.03</td>
<td>2.68 ± 0.02</td>
<td>2.96 ± 0.02</td>
<td>2.96 ± 0.02</td>
<td>3.09 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>PE(mBP)</td>
<td>2.91 ± 0.03</td>
<td>2.91 ± 0.03</td>
<td>2.91 ± 0.03</td>
<td>2.91 ± 0.03</td>
<td>3.09 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>PE(SV)</td>
<td>2.94 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>3.09 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>PE(CO)</td>
<td>2.94 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>2.94 ± 0.02</td>
<td>3.09 ± 0.01</td>
<td></td>
</tr>
</tbody>
</table>

SE - standard error, Δ – difference between mean baseline value and after 31 hours of TSD, CI – Confidence Interval of the difference between means, RRI – R-R interval, HR – Heart Rate,


As table 4 shows, significant increase of LFnu-sBP responsiveness to HUT in the 31-h of TSD (-1.97 during baseline vs -10.69, F = 14.8, p = 0.0004, \( \omega^2 = 0.27 \)). HFnu-dBP decrease in response to HUT after 31-h of TSD (5.94 during baseline vs 6.66 after 31-h TSD Z = 4.16, p = 0.00003, r = 0.43). PE(mBP) responsiveness to HUT tended to decrease in response to HUT in the baseline and increase to HUT after 31-h of TSD (0.13 during baseline vs -0.07), F = 4.36, p = 0.04, \( \omega^2 = 0.32 \). Statistically significant differences between baseline and 31-h TSD in parameters measured in response to HUT are shown of Figure 6.
Figure 6. Differences in baseline vs after 31-h TSD in response to HUT. Red dots connected by red line indicates mean value, horizontal black line inside the box denotes median value. Green dots during baseline and orange dots after 31 hours of total sleep deprivation connected by dashed lines denotes results of individual subjects. Shape of violin graph indicates distribution of values.
Table 4. Physiological parameters in response to HUT. Differences between mean value in supine and during HUT is provided. Mean ± SE values are provided in the baseline. P value is result of repeated measured ANOVA or Wilcoxon signed-rank test.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline±SE</th>
<th>Δ</th>
<th>CI -95%</th>
<th>CI 95%</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td>RRI</td>
<td>190.05±17.55</td>
<td>-1.20</td>
<td>162.37</td>
<td>220.14</td>
<td>0.84</td>
</tr>
<tr>
<td>HR</td>
<td>-13.31±1.14</td>
<td>1.25</td>
<td>-16.65</td>
<td>-12.48</td>
<td>0.22</td>
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<tr>
<td>sBP</td>
<td>-17.70±1.85</td>
<td>-1.83</td>
<td>-17.81</td>
<td>-13.92</td>
<td>0.38</td>
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<tr>
<td>dBP</td>
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<td>-24.00</td>
<td>-19.98</td>
<td>0.54</td>
</tr>
<tr>
<td>mBP</td>
<td>-20.75±1.6</td>
<td>-1.08</td>
<td>-21.53</td>
<td>-17.80</td>
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<tr>
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<td>28.60±3.32</td>
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<td>24.64</td>
<td>36.52</td>
<td>0.52</td>
</tr>
<tr>
<td>CO</td>
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<td>-0.10</td>
<td>0.39</td>
<td>1.07</td>
<td>0.60</td>
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<tr>
<td>LVET</td>
<td>36.77±2.79</td>
<td>1.07</td>
<td>31.49</td>
<td>39.91</td>
<td>0.61</td>
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<td>LFnu-RRI</td>
<td>-16.25±2</td>
<td>2.03</td>
<td>-22.22</td>
<td>-14.34</td>
<td>0.38</td>
</tr>
<tr>
<td>HFnu-RRI</td>
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<td>-2.03</td>
<td>14.34</td>
<td>22.22</td>
<td>0.38</td>
</tr>
<tr>
<td>LF/HF-RRI</td>
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<td>-3.93</td>
<td>-2.08</td>
<td>0.45</td>
</tr>
<tr>
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<td>-2.25</td>
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<td>-0.97</td>
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<td>-1.02</td>
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<td>6.66</td>
<td>-5.53</td>
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<tr>
<td>FD(RRI)</td>
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<td>0.00</td>
<td>0.21</td>
<td>0.29</td>
<td>0.98</td>
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<tr>
<td>FD(HR)</td>
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<td>0.00</td>
<td>0.21</td>
<td>0.29</td>
<td>1.00</td>
</tr>
<tr>
<td>FD(sBP)</td>
<td>0.06±0.02</td>
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<td>0.04</td>
<td>0.11</td>
<td>0.35</td>
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<tr>
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<td>0.12</td>
<td>0.74</td>
</tr>
<tr>
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<tr>
<td>FD(SV)</td>
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<td>0.01</td>
<td>0.09</td>
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<tr>
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<tr>
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<tr>
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<td>0.39</td>
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<tr>
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<td>PE(dBP)</td>
<td>PE(mBP)</td>
<td>PE(SV)</td>
</tr>
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<td>------------</td>
<td>------------</td>
<td>------------</td>
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<td>------------</td>
</tr>
<tr>
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<td>0.21±0.02</td>
<td>0.22±0.04</td>
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<td>0.11</td>
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<td>±0.03</td>
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<tr>
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<td>0.15–0.25</td>
<td>0.19–0.30</td>
<td>0.13–0.27</td>
<td>0.11–0.76</td>
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</table>

Discussion

In our investigations we denoted statistically significant differences between some recorded signals in baseline and after 31-h of TSD. In supine positions we observed increase of HR and decrease of RRI and LVET. The increase of non-linear measures of mBP was indicated by two methods, namely PE and AAPE. In response to HUT, blood pressure values processed by autoregressive method (normalized units of high frequency of dBP and low frequency of sBP) was altered. Permutation entropy of mBP in response to HUT was significantly different after 31-h of TSD.

LVET is a widely used parameter in the assessment of the autonomic nervous system in physiological studies in response to emotional stimuli (Kreibig 2010). Therefore, the observed increase of supine HR seen in our study with the accompanied decrease of RRI and LVET after 31 hours of TSD could reflect increased sympathetic modulation of heart rhythm during rest in the supine position. Previous studies (Glos et al. 2014) have observed higher LF/HF ratio during daytime when under conditions of increasing sleep loss which reflects elevated cardiac sympathetic modulation. However, what should be underlined, Glos et al. have used standard deviation of NN intervals and the root mean square of successive differences and 12-pole AR spectral analysis methods. Moreover, Viola et al. (Viola et al. 2008) have found a similar trend towards LF/HF increase using similar methods as Glos et al with addition of the percentage of the number of times consecutive normal sinus (NN) intervals exceeded 50 ms. Additionally, a steady increase in LF/HF ratio during the performance of a reaction-time task when influenced by sleep deprivation at multiple time points has been observed (Zhong 2005). Interestingly, LF/HF was not significantly influenced by TSD in our sample. Moreover, statistically significant increases in in AAPE (mBP), and PE (mBP) whilst supine were observed after 31-h
of TSD compared to baseline. This results might imply stability loss of system controlling blood pressure (Wagner et al. 1996). In our opinion these changes could reflect autonomic nervous system modulation which extends beyond the influence upon cardiac activity alone. For example, studies (Jartti et al. 1998) have shown a dose–response effect of terbutaline, an β2 adrenergic receptor agonist, not only on indicators of cardiac functioning (decreased total, LF and HF variability and approximate entropy and FD of RRI) but also modulated total and HF variability and approximate entropy of sBP. Moreover, significant changes of normalized units of low frequency and high frequency of systolic and diastolic blood pressure, respectively were observed. In addition, values of PE(mBP) in response to HUT were significantly influenced by 31 hours of TSD. Interestingly, while all entropy analysis revealed significant changes of mBP whilst supine in consecutive time points of TSD, only permutation entropy revealed significant changes in response to HUT along with changes of values of spectral analysis. Therefore, it could be concluded that permutation entropy could be useful in the examination of a biosignals response to HUT. Buszko et al. (Buszko et al. 2017) have described an application of entropy of RRI, sBP, dBP and SV in the diagnosis of vasovagal syndrome. The loss of complexity of heart rhythm, BP and SV in the pre-syncope phase could be an indicator of the development of a neuro-cardiogenic reaction (Buszko et al. 2017). In our study was denoted increase AAPE(mBP) and PE(mBP) whilst supine, there was a significant decrease in PE(mBP) in response to HUT observed after 31 hours of TSD compared to the baseline. However, no significant changes in results of FD analysis was noted in supine nor in response to HUT after TSD. In contrast to the above results, acute physical exercise decreased results of Higuchi FD analysis of heart rate (Gomes et al. 2017). However, physical exercise is related to very different pattern of muscle contractions comparing to undergoing HUT, what induce different cardiovascular system reaction and presumably might explain difference in
observed results (Kondo et al. 2018, Egesborg et al. 2018). Therefore, it could be assumed that decreased entropy of biosignals could characterize a pathological reaction to HUT, which could be also observed in a vasovagal reaction (Buszko et al. 2017) as well as after the 31 hours of TSD. Turianikova et al. (Turianikova et al. 2011) showed that orthostatic stress alters autonomic nervous system regulation which could be reflected by changes in entropy, however these studies did not involve autoregressive method (Turianikova et al. 2011). We would suggest that studies using linear methods may not be sufficiently sensitive to detect modulation of ANS.

The participant group included in our study could be considered as homogenous (same-profession, men only) who are used to working in a TSD-environment. Viola et al., have also investigated a men only group (Viola et al. 2008) in contrast to other studies that have included mixed groups (Glos et al. 2014; Zhong et al. 2005). Gender differences in the groups examined could potentially affect the results due to the tendency for higher HRV values in men compared to women, especially in the relatively young (Bonnemeier et al. 2003), and by the reduced vulnerability to sleep pressure in men than women (Birchler-Pedross et al. 2009). Interestingly, it has been shown that male shift-workers have higher LF values during SD than non-shift workers (Wehrens et al. 2012).
Conclusions

TSD alters autonomic nervous system modulation of cardiac and vascular functioning while supine and in response to orthostatic stress. TSD resulted in changes in cardiac and both spectral and two entropy analysis of blood pressure when supine. Values of spectral analysis of blood pressure and permutation entropy of mean blood pressure in response to HUT were significantly changed after 31 h of TSD. Interestingly, the dynamics of measured parameters obtained analyzed PE and AAPE was rather similar, therefore it could be concluded that the changes of complexity of analyzed signals revealed by these methods were consistent during TSD.

Surprisingly, no statistically significant differences between baseline and the following time points of TSD were observed in the rest of parameters during supine nor in response to HUT.

It can be concluded that TSD alters autonomic nervous system modulation of functioning of several organs during supine and while orthostatic stress. Interestingly, differences in pattern of changes of parameters during TSD were observed between supine and in response to HUT test. TSD resulted in changes in cardiac and both spectral and nonlinear parameters analysis of blood pressure during the supine, while in the response to HUT only values of spectral analysis of blood pressure and permutation entropy of mean blood pressure were altered. Therefore, used entropy analysis methods gave rather consistent pattern of results in the consecutive time points of TSD in supine position, while in response to HUT only permutation entropy values were altered.
Acknowledgements

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Author Contribution

Sławomir Kujawski: Conceptualization, Software, Validation, Formal analysis, Data Curation, Writing - Original Draft, Writing - Review & Editing Katarzyna Buszko; Software, Validation, Data Curation, Writing - Review & Editing Agnieszka Cudnoch-Jędrzejewska: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Joanna Słomko: Conceptualization, Validation, Investigation, Data Curation, Writing - Review & Editing, Project administration, Djordje G Jakovljevic: Writing - Review & Editing, Julia L. Newton: Writing - Review & Editing, Pawel Zalewski: Conceptualization, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of Collegium Medicum in Bydgoszcz research ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.