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Original Article

Preserved cardiac autonomic dynamics during sleep in subjects with spinal cord injuries

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ABSTRACT

Background: Spinal cord injuries (SCI) are associated with altered cardiovascular autonomic control (CAC). Sleep is characterized by modifications of autonomic control across sleep stages; however, no data are available in SCI subjects on CAC during sleep. We aim to assess cardiac autonomic modulation during sleep in subjects with SCI.
Patients and methods: 27 participants with a neurological and radiological diagnosis of cervical (Cerv, $n = 12$, ie, tetraplegic) and thoracic SCI (Thor, $n = 15$, ie, paraplegic) and healthy subjects (Controls) were enrolled. Overnight polysomnographic (PSG) recordings were obtained in all participants. Electrocardiography and respiration were extracted from PSG, divided into sleep stages [wakefulness (W), non-REM sleep (NREM) and REM] for assessment of CAC, using symbolic analysis (SA) and corrected conditional entropy (CCE). SA identified indices of sympathetic and parasympathetic modulation and CCE evaluated the degree of complexity of the heart period time series.
Results: SA revealed a reduction of sympathetic and predominant parasympathetic control during NREM compared to W and REM in SCI patients, independent of the level of the lesion, similar to the Controls. In all three groups, complexity of autonomic regulation was higher in NREM compared to W and REM.
Conclusions: In subjects with SCI, cardiac autonomic control changed across sleep stages, with a reduction of sympathetic and an increase of parasympathetic modulation during NREM compared to W and REM, and a parallel increase of complexity during NREM, which was similar to the Controls. Cardiac autonomic dynamics during sleep are maintained in SCI, independent of the level of the lesion.

1. Introduction

Spinal cord injuries (SCI) are a major cause of disabilities among young populations all over the world, with more than 200 million individuals living with chronic neurological disabilities due to SCI [1].

Over the past decade, several studies have demonstrated that subjects with SCI have an increased cardiovascular risk [2–5]. In fact, abnormalities in heart rate (HR) and blood pressure (BP) control, together with increased prevalences of obesity, dyslipidemia, and altered glucose metabolism have been described in this population and are responsible for a worse cardiovascular-risk profile. It has also been shown that alterations of cardiovascular autonomic control could play an important role in this setting. However, it is not known whether this autonomic dysregulation may affect cardiovascular and autonomic dynamics occurring during sleep.

Analysis of heart rate variability (HRV), a non-invasive tool to evaluate autonomic cardiovascular regulation in health and disease [6,7], revealed significant changes of sympatethic and parasympathetic control in people with SCI. In fact, several studies described important modifications of rhythmical components of HRV representing sympathetic and parasympathetic control in patients with both cervical and thoracic SCI, sometimes reporting contrasting findings [8–13]. However, it is believed that no studies have evaluated cardiac autonomic control during sleep in people with SCI.

Recently, new non-linear methods, such as symbolic dynamics and entropy-derived measures, have been proposed as valid tools

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that are able to overcome important technical limitation of spectral analysis and are capable of providing complementary information on the neural mechanisms that control and regulate cardiac sinus node function [14–20]. Symbolic analysis (SA) is a novel non-linear tool for the assessment of HRV that has been validated in health and pathological conditions [14,15,19–21]. Symbolic analysis seems to be more reliable than other classical linear tools in conditions characterized by low total variability, and it is capable of detecting non-reciprocal changes of the two autonomic branches; for instance, before the onset of major ventricular arrhythmias, SA detected an increase of sympathetic control with no changes in parasympathetic modulation, thus suggesting a possible coactivation of the two autonomic branches in this setting [21].

On the other hand, corrected conditional entropy (CCE) is a non-linear tool derived from entropy analysis that has already been used to assess autonomic cardiac complexity during wake and sleep [19,20,22]. Entropy measures provide complementary information to classical spectral tools, evaluating the complexity of the cardiovascular autonomic control. A reduction of complexity, such as during aging and diseases, suggests that different control systems that regulate a certain variable (ie, sinus node function) do not interact and co-operate, but once a mechanism becomes predominant it leads to a simplification of the cardiovascular control and to an impaired capability to response to stressor stimuli.

Hence, the aim of the present study was to assess cardiac autonomic modulation in subjects with SCI using new non-linear tools (ie, symbolic and entropy analysis) during wakefulness and through sleep stages, taking into consideration the site of the lesion.

2. Methods

2.1. Study population and experimental protocol

The study was approved by the IRB of the Niguarda Ca' Granda Hospital and informed consent was signed by all participants.

From November 2010 to December 2011, 27 people with a neurological and radiological diagnosis of cervical (Cerv, $n = 12$, ie, tetraplegic) and thoracic (Thor, $n = 15$, ie, paraplegic) SCI were consecutively enrolled. A group of people without SCI, who were matched for age, gender, and body mass index (BMI) with the SCI group, was enrolled as a control group at the Mayo Clinic, Rochester, Minnesota (Controls, $n = 8$). The unique exclusion criteria were the absence of sinus rhythm due to atrial fibrillation, excessive supra or ventricular premature beats (more than 5% of the entire recording) or pacemaker rhythm.

Each participant underwent a complete polysomnographic study (PSG) during hospitalization at the Department of Neurosciences, 'Niguarda Ca' Granda' Hospital, Milan, within a mean time of 65 days from the injury. Standard, overnight, full PSG was performed on the ward in an attended setting (AURA®; PSG Ambulatory Systems GRASS Technologies, USA). In accordance with standard criteria, the recording included: electroencephalography (at least three channels, frontal, central and occipital); bilateral electro-oculography; chin and bilateral tibial electromyography; electrocardiography (ECG); oronasal airflow; chest and abdominal effort; pulse oximetry; and sensor of body position. A doctor specialized in sleep medicine and was certified by the Italian Association of Sleep Medicine reviewed all studies. Sleep was staged and respiratory and motor events were visually scored according to current standard criteria [23]. Motor and sensory examinations were performed and all patients were classified using the ASIA impairment scale A–D [24].

2.2. Data analysis

From PSG recordings, ECG and respiratory traces were extracted using an ad hoc off-line program and then divided into wakefulness (W), non-REM sleep 2 (N2), non-REM sleep 3 (N3), and REM. The first two complete sleep cycles of the night for each participant (NREM and REM sleep) were selected for the analysis.

The respiratory traces were carefully checked and any periods with apneas/hypopneas or irregular breathing were excluded from the analysis; thus, only those ECG segments associated with stable and regular breathing were considered.

The QRS complexes were identified and parabolic interpolation was used to locate the apex of the R waves. All the ECG traces were linearly detrended and carefully checked to avoid any missing beats and any incorrect detection of QRS complexes.

Samples of consecutive 250–300 beats were identified according to the sleep stages (W, N2, N3 and REM) for each group and off-line algorithms were applied for the assessment of HRV (ie, symbolic analysis and corrected conditional entropy).

Respiratory traces were resampled at 512 Hz and the respiratory rate was assessed from the respiratory signal.

2.3. Non-linear analysis of heart rate variability

2.3.1. Symbolic analysis

A full description of the mathematical details of SA algorithms is furnished elsewhere [19,20]. Briefly, SA is based on: (1) the transformation of time series into a sequence of symbols; (2) the construction of patterns using these symbols (ie, words); (3) the reduction of the number of patterns into four families; and (4) the evaluation of their rate of occurrence expressed as percentages. Therefore, all patterns are grouped without any loss into four categories: 0V, pattern with no variation (ie, all the symbols are in the same level); 1V, pattern with one variation (two consecutive symbols are equal and the remaining one is different); 2LV, patterns with two like variations (the three symbols form an ascending or descending ramp); and 2UV, pattern with two unlike variations (the three symbols are organized forming a peak or a valley). As stated above, the rate of occurrence of the patterns is expressed as a percentage (ie, 0V%, 1V%, 2LV%, and 2UV%). Experimental and pharmacological studies have shown that category 0V is a marker of sympathetic modulation, while the categories 2LV and 2ULV are considered to be markers of parasympathetic modulation [14,15,19–21].

2.3.2. Corrected conditional entropy

Corrected conditional entropy can be derived from conditional entropy, which evaluates the amount of information carried by the current RR sample [ie, RR(i)] when L-1 past samples of RR are known [ie, $RR_{L-1}(i\text{-}1) = (RR(i\text{-}1)\ldots RR(i\text{-}L+1)]$. In other words, CE represents the difficulty in predicting future values of a time series when the past values are known. For the CE estimation, RR series are uniformly quantized over $\xi = 6$ bins (number optimized to deal with short data sequences). However, because the calculation of CE is biased, CCE was designed to overcome these mathematical limits. CCE decreases to 0 when the new sample is fully predictable, reaches its maximum value when the new sample is completely unpredictable, and reaches its minimum value when the knowledge of past values is helpful to reduce the uncertainty associated with future values.

2.4. Statistical analysis

Data are presented as mean ± SD. SigmaPlot 12 (Systat Software Inc., Chicago, IL, USA) was used for statistical analysis. A two-way analysis for variance (ANOVA) was used to check the differences between the groups within the sleep stages. The normality test (Shapiro–Wilk test) was applied to check the normality of the distribution; if this was not the case, an equal variance test was performed. A Holm–Sidak method for all pair-wise