Clinical Neurophysiology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Autonomic imbalance during apneic episodes in pediatric obstructive sleep apnea

Ottavio Vitelli, Marco Del Pozzo, Giorgio Baccari, Jole Rabasco, Nicoletta Pietropaoli, Mario Barreto, Maria Pia Villa *

Neuroscience, Mental Health and Sense Organs Department, Sleep Disorder Centre, Faculty of Medicine and Psychology, "La Sapienza" University, Rome, Italy

ARTICLE INFO

Article history:
Accepted 27 May 2015
Available online xxxx

Keywords:
Autonomic nervous system
Obstructive sleep apnea
Children
Heart rate variability
Pediatric
Autonomic impairment

HIGHLIGHTS

- R-apnea index evaluates heart rate variability during apnea and it is a new and easy method to underlay early cardiac autonomic nervous system (ANS) imbalance in children with obstructive sleep apnea (OSA).
- OSA severity and the duration of the disease significantly correlate with R-apnea index.
- Cardiac ANS imbalance is present in children with OSA.

ABSTRACT

Objectives: To investigate the activity of the autonomic nervous system (ANS) during sleep in children with obstructive sleep apnea (OSA), in order to detect a possible cardiac ANS imbalance analyzing heart rate variability (HRV).
Methods: 43 subjects between 4 and 12 years of age (7.26 ± 2.8 years), undergoing a diagnostic assessment for OSA were evaluated. A time domain index (R-apnea index) was developed to evaluate HRV strictly related to obstructive events during sleep. Poincaré plot of RR intervals during the whole night was calculated.
Results: R-apnea index was negatively correlated with apnea hypopnea index (AHI) ($r = -0.360$, $p = 0.028$). AHI and the duration of the disease were the only variables that were significantly correlated with R-apnea index. Three groups were subsequently created according to polysomnographic findings considering AHI. R-apnea index resulted significantly lower in patient with severe OSA compared to primary snoring/mild OSA subjects ($p < 0.05$). Looking at Poincaré plot, SD1 showed a diminishing trend with severity of OSA, however not reaching statistical significance.
Conclusions: Our findings suggest an autonomic impairment in OSA children evidenced by the altered HRV both in the very short term (R-apnea index) and in short term (SD1).
Significance: R-apnea index is an easy and cheap method to undelay early ANS imbalance.

1. Introduction

Obstructive sleep apnea (OSA) is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction (hypopnea) and/or intermittent complete obstruction (obstructive apnea) that disrupt normal ventilation during sleep and normal sleep patterns (Marcus et al., 2012). OSA may affects children of all ages, from newborns to adolescents, with a higher prevalence in preschool age, and with a peak of incidence between 2 and 6 years of age (Jeans et al., 1981; Arens et al., 2002). Prevalence rates range from 1.2% to 5.7% according to the different studies (Marcus et al., 2012; Bixler et al., 2009; Li et al., 2010; O'Brien et al., 2003).

A prompt diagnosis and treatment of OSA is very important because it is associated with several comorbidities, such as neuro-cognitive and behavioral anomalies (Gozal, 1998; Gozal et al., 2007a,b); cardiovascular dysfunction such as systemic and pulmonary hypertension (Sans Capdevila et al., 2008; Amin et al., 2004; Marcus et al., 1998); cardiac remodeling (Amin et al.,

* Corresponding author at: Sleep Disorder Centre, Sant'Andrea Hospital, Via Grottarossa 1035-1039, 00189 Rome, Italy. Tel.: +39 0633775855; fax: +39 0633775941.
E-mail address: mariapia.villa@uniroma1.it (M.P. Villa).

http://dx.doi.org/10.1016/j.clinph.2015.05.025
1388-2457/

2008); endothelial dysfunction (Gozal et al., 2002, 2007a,b); and metabolical alterations (Bhattacharjee et al., 2011).

Autonomic dysfunction is thought to play a key role in a majority of OSA complications, especially in the development of cardiac consequences of both adult and pediatric patients affected by OSA, since the cardiovascular system is highly regulated by the autonomic nervous system (ANS) (Bonsignore et al., 2002; Vlahandonis et al., 2013).

In recent years, the analysis of heart rate variability (HRV) has become increasingly used as non-invasive method for analyzing cardiovascular autonomic modulation. HRV is defined as the variation of the time period between consecutive heart beats, and it is thought to reflect the heart's adaptability to the changing physiological conditions. In addition, HRV is useful to understand the balance between the sympathetic ANS, that serves to speed up the heart rate (HR) and parasympathetic ANS, that slows down the HR (Akselrod et al., 1981).

The physiological autonomic changes are expressed by different tools, such as time-domain indices providing estimates of overall and beat-to-beat variability; frequency-domain analysis, which is based on the power spectral density of the HR time series and highlights the issue of the underlying rhythms of the mechanisms controlling HR; and other complex techniques known as non-linear methods (Rosenstock et al., 1999). Poincaré plot is a visual representation of HRV on a Cartesian plane and it is one of the commonly used non-linear methods of HRV analysis (Kamen et al., 1996; Brennan et al., 2002) (Fig. 1). It has various non-linear elements (i.e., short-term variability [SD1] and long-term variability [SD2]) that have been linked to parasympathetic modulation (Karmakar et al., 2011; Brennan et al., 2002).

Typically during the onset of apnea, there is a progressive bradycardia followed by a sudden tachycardia when the apnea ends. This transiently increases the variability in both HR and blood pressure (Penzel et al., 2003; O'Driscoll et al., 2009). An impairment in this HRV may indicate an impairment in cardiovascular autonomic modulation.

Since the autonomic consequences of OSA lead to a progressive sympatho-vagal imbalance, we hypothesized that an altered ANS activity, as a cardiovascular response to apnea during sleep, could be the first sign of autonomic deregulation in a cohort of children with OSA. A simple, economic and event related time-domain index of HRV and Poincaré plot analysis, have been used.

2. Methods

2.1. Study subjects

From January 2012 to September 2013, children between 4 and 12 years of age, who were undergoing a diagnostic assessment for OSA in our Paediatric Sleep Centre (Rome, Italy), were enrolled in the study. Exclusion criteria included: previous diagnosis or treatment for OSA, epilepsy, acute or chronic cardiorespiratory or neuromuscular diseases, dysmorphism, chronic inflammatory diseases, major craniofacial abnormalities, and chromosomal syndromes.

Written informed consent was obtained from parents and verbal assent from the children before enrollment in the study. The study was approved by the Ethics Committee of the Sant'Andrea Hospital.

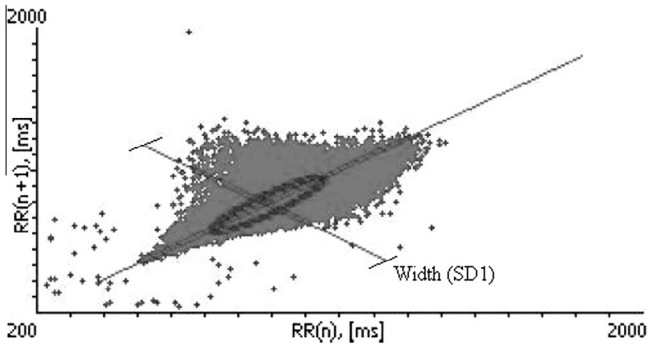

Fig. 1. Cartesian plane illustrating the Poincaré plot of sequential R–R intervals derived from the electrocardiographic channel of polysomnography during the whole night of sleep.

2.2. Clinical and polysomnographic evaluation

A detailed personal and family history was obtained for all the participants. A general clinical examination was performed. A detailed parental interview about symptoms and duration of OSA and family history of cardiovascular diseases was also obtained. Heights, weight, blood pressure of each child were measured using standard techniques. Body mass index (BMI) was then calculated (body mass/height^2). Obesity was diagnosed according to the International Obesity Task Force and was defined as $\geqslant$ the 95° percentile of the BMI (pBMI) (Cole et al., 2000).

After a night of adaptation in the hospital, all participants in the study underwent in-bed unattended sleep recordings, using SOMNOscreen™ polysomnography device (SOMNOmedics GmbH, Randersacker, Germany). The following leads were applied: two electrooculogram leads to the right and left outer canthi, leg (tibialis) electromyograms; nasal pressure transducer and oral thermistor to assess airflow; electrocardiogram (one derivation), chest and abdominal piezo-belts to measure respiratory effort; and a finger oximeter to measure oxyhemoglobin saturation, as well as a microphone to assess snoring. All recordings started at the patients' usual bedtime and continued until spontaneous awakening. Respiratory events were manually scored according to the criteria established by the AASM using DOMINO-Software (DOMINO 2.4.0 supplied with the SOMNOscreen™) (Iber et al., 2007). Central, obstructive, mixed apnea and hypopnea events were scored. The apnea–hypopnea index (AHI) was defined as the average number of apneas and/or hypopneas per hour of sleep.

2.3. Heart rate variability analysis

HRV was evaluated in relation to obstructive events during sleep, according to a time domain index: the R-apnea index. This was calculated as an average of at least a minimum of three measurements during apneic events, randomly selected, during REM and nREM sleep. All the measurements corresponding to the definition were considered. Each measurement was the ratio of the longest RR interval during an obstructive apneic event of at least 10 s, to the shortest RR interval in a period of the same duration of the apnea after its ending (Fig. 2) (i.e., the longest RR interval was evaluated during a 12 s long obstructive apnea and then the shortest RR interval was evaluated in the subsequent 12 s). This index was similar to one previously used in adult patients by Ferini-Strambi et al. (1992), but is has been slightly modified in order to better apply to pediatric apneas (selecting events of at least 10 s instead of 20 s).

The Poincaré plot of RR intervals from the whole night of recordings was automatically calculated by the DOMINO-Software. The width of the Poincaré plot (SD1) was used for short term variability (i.e., 5–30 min) while long-term variability (i.e., 24 h) corresponded to the length of the graph (SD2) (Karmakar et al., 2011).

2.4. Statistical analysis

All variables were tested for normality of distribution using the Kolmogorov–Smirnov test. Values were expressed as arithmetic

Please cite this article in press as: Vitelli O et al. Autonomic imbalance during apneic episodes in pediatric obstructive sleep apnea. Clin Neurophysiol (2015), http://dx.doi.org/10.1016/j.clinph.2015.05.025