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Effects of CPAP on clinical variables and autonomic modulation in children during an asthma attack

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ABSTRACT

Continuous positive airway pressure (CPAP) causes changes in alveolar and intrathoracic pressure and the activation of pulmonary stretch receptors affects the balance of the autonomic nervous system. The acute effects of CPAP on autonomic modulation have been demonstrated in different diseases, but no studies have been carried out addressing CPAP in patients with asthma. The hypothesis tested in the present study is that CPAP can produce an autonomic effect beyond a mechanical effect of bronchial dilatation in children with asthma. The results demonstrated improvements in clinical variables and an increase in vagal tone with the administration of CPAP during an asthma attack, as demonstrated by a diminished respiratory rate and a reduction in signs of respiratory distress. Regarding autonomic modulation, an increase in parasympathetic variables was found, indicating non-cholinergic activation stemming from the persistent increase in peak flow.

1. Introduction

The bronchial obstruction and hyperinflation caused by an asthma attack predispose children to respiratory failure. The management of severe acute asthma involves the correction of hypoxemia, alleviation of air-flow obstruction and the suppression of inflammation with medication.

Continuous positive airway pressure (CPAP) is employed to reduce the respiratory muscle work imposed by hyperinflation and promote changes in autonomic modulation (Fessler et al., 1995; Reis et al., 2010). There is evidence of the efficacy of noninvasive ventilation (Bilevel and CPAP) in acute asthma, with reports of decreased respiratory work, accelerated recovery of lung function, diminished bronchodilator dose and shorter duration in the intensive care unit and hospital among adults with acute asthma treated with noninvasive ventilation (Gupta et al., 2010; Lin et al., 1995; Shivaram et al., 1987; Martin et al., 1982).

CPAP causes changes in alveolar and intrathoracic pressure and the activation of pulmonary stretch receptors exerts an influence on autonomic modulation (Canning, 2006; Reis et al., 2010). In an animal model, Xue et al. found that the increase in intrathoracic pressure leads to a reduction in bronchial responsiveness (exaggerated airway response to a bronchial stimulus) that can persist for up to 24 h after the removal of CPAP. In adults with stable asthma, CPAP reduced bronchial responsiveness and was considered a no pharmacologic intervention to decrease airway reactivity (Lin et al., 1995; Busk et al., 2013).

Children with asthma experience changes in autonomic modulation (Fuji et al., 2000; Emin et al., 2012), with an increase in bronchial sensitivity to cholinergic constrictors and possibly a reduction in sensitivity to β_2 adrenergic bronchodilators. Parasympathetic nerve stimulation can result in both contraction and relaxation of the bronchial muscles. Contraction is mediated by acetylcholine and relaxation is mediated by non-adrenergic and non-cholinergic transmitters. Cholinergic tone is remarkably sensitive to the mechanism of ventilation, undergoing a decrease with the reduction in respiratory rate (Canning, 2006).

The acute effects of CPAP on autonomic modulation have been demonstrated in different diseases in adults such as COPD and heart failure (Reis et al., 2010), but no studies have been carried out addressing CPAP in patients with asthma. The hypothesis tested herein is that CPAP can produce an autonomic effect beyond a mechanical effect of bronchial dilatation.

Heart rate variability (HRV) is the most frequently used non-invasive method for assessing autonomic modulation and its

Abbreviations: fH, heart/cardiac frequency; HRV, heart rate variability; fR, respiratory rate/frequency; PI, pulmonary index; SDRR, standard deviation in mean of R-R intervals; RMSSD, square root of the sum of squared differences between R-R intervals; LF, low frequency; HF, high frequency; SD, standard deviation; DFA, detrended fluctuation analysis; ApEn, approximate entropy; S_{O_2}, oxygen saturation; CPAP, continuous positive airway pressure.

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influence on the cardiovascular system. Thus, HRV is valuable in providing information on the heart's ability to respond to normal regulatory impulses that affect its rhythm (Task Force, 1996).

The aim of the present study was to evaluate clinical alterations and changes in autonomic modulation promoted by CPAP in children during an asthma attack.

2. Materials and methods

2.1. Study design

A prospective cross-sectional study was carried out involving children on the first day of hospitalization due to an asthma attack. The evaluation consisted of laboratory exams and the acquisition of data on heart rate variability (HRV) measured in the supine position (with 30° elevation) for 10 min, during the administration of CPAP for 20 min and for an additional 10 min following CPAP.

2.2. Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and received approval from the Human Research Ethics Committee of Nove de Julho University (Brazil) under protocol number 77913/2012. Parents/guardians of the participants signed a statement of informed consent.

2.3. Subjects

The sample was composed of 19 children (12 boys and 7 girls aged 5–12 years) evaluated on the first day of hospitalization at the pediatric emergency ward of the Mandaqui Hospital (São Paulo, Brazil) in the period spanning August–October 2012. The participants had a medical diagnosis of asthma and were in regular follow up with specialists. The children were diagnosed by pulmonologists based on the classification proposed in the guidelines of the Global Initiative for Asthma (GINA, 2011) and Guidelines for the Diagnosis and Management of Asthma (2007).

2.4. Data collection

2.4.1. Autonomic nervous system tests

CPAP (Vygon™) was performed with a face mask with pressure of 10 cm H_2O for 20 min (Reis et al., 2010; Busk et al., 2013). HRV was assessed simultaneously using a Polar™ RS800CX monitor. The measures of HRV were performed in the supine position with 30° elevation.

The HR data were transferred to the microcomputer and the RRi series were reviewed by visual inspection. Only segments with >90.0% pure sinus beats were included in final analysis. The data were entered into Kubios HRV analysis software (MATLAB, version 2 beta, Kuopio, Finland) and HRV analysis proceeded with one series of 300 sequential RRi.

The following time domain indices were evaluated: mean heart rate (HR), mean of all normal R-R intervals, standard deviation of R-R intervals (STDRR) and root mean square of successive differences between normal sinus R-R intervals (RMSSD). The following frequency domain indices were evaluated: low frequency (LF; 0.04–0.15 Hz), high frequency (HF; 0.15–0.4 Hz) and LF/HF ratio. To summarize, STD RR represents a global index of HRV (overall HRV) and reflects all the cyclic components responsible for variability in the recording period, RMSSD reflect alterations in autonomic tone that are predominantly vagally mediated and the geometrical HRV indexes are an estimate of the overall HRV (Mendes et al., 2011; Acharya et al., 2004).

The non-linear properties of HRV were analyzed using measures such as approximate entropy (ApEn), correlation dimension (CD) and Poincaré plot. ApEn quantifies the regularity of time series data and is represented as a simple index for the overall complexity and predictability of each time series. Large values of ApEn indicate high irregularity and smaller values of ApEn indicate a more regular signal. Thus, the highest ApEn value reflects better health and function (Pincus, 1991; Pikkujämsä et al., 1999; Cysarz et al., 2011).

The CD index represents a measure of the dimensionality of the space occupied by state vectors or the number of the degrees of freedom of a time series, also referred to as fractal dimension. A higher CD reflects more degrees of freedom of the cardiac pacemaker and, therefore, the greater the range of possible adaptive responses to internal or external stimuli in an ever-changing environment.

The non-linear analysis of the Poincaré plot of RRi was applied and the following two descriptors of the Poincaré plot were used in the study: SD1 – the standard deviation measuring the dispersion of points in the plot perpendicular to the line-of-identity. This parameter is usually interpreted as a measure of short-term HRV, which is caused mainly by respiratory sinus arrhythmia (parasympathetic modulation); and SD2 – the standard deviation measuring the dispersion of points along the identity line, which is interpreted as a measure of both short and long-term HRV (overall HRV) (Okamoto et al., 2011; Acharya et al., 2004).

Intermediate-term and short-term fractal scaling-like correlation properties of the R-R interval series were quantified using DFA (detrended fluctuation analysis). The fluctuations of the integrated and detrended R-R interval series depend on the chosen window size. If log (fluctuations) is plotted against log (window size) linear relationships appear in two different regions. The slope of the linear relationship is referred to as scaling exponents a1 (windows size: 4–11 beats) and a2 (windows size: 0.11 beats) indicating short and intermediate-term correlations (Schubert et al., 2009; Piskorski and Guzik, 2007).

2.4.2. Clinical signs and laboratory data

The children were placed in the supine position with 30° elevation and the procedure was explained to them. The following variables were determined: respiratory rate (fR) in 60 s; peripheral oxygen saturation (S_{O_2}) using a Clinical Guard™ pulse oximeter at room air; heart rate (fH) using the Polar RS800CX™ monitor; and peak flow using the Access™ equipment. For peak flow, three measurements were taken in the sitting position with a nasal clip and the highest was considered. All measurements were determined before and immediately after CPAP. HRV was also measured during CPAP. The evaluations were performed at least 8 h following bronchodilator use to avoid the acute effect of medication on the measurement of peak flow. C-reactive protein (CRP) was determined as an inflammatory marker upon admission to the pediatric emergency ward.

The severity of the crisis was evaluated by pulmonary index (PI) (Scarfone et al., 1993), score that evaluates clinical parameters such as fR, fH, S_{O_2}, wheezing, I:E relationship and use of accessory muscles. Increased score indicates greater severity of symptoms and the score can range between (0 and 15).

2.4.3. Sample calculation and statistical analysis

The sample size was calculated based on the results of a pilot study involving six children. Considering a standard deviation of 20.0 to detect a difference of 13.0 in the RMSSD, β error of 0.2 and α error of 0.05, the minimum sample size was determined to be 15 patients.

The data were analyzed using the Minitab 14.0 program. ANOVA with Tukey's post hoc test was used for the comparison of the variables among the three evaluation times (before, during and after CPAP). The Kolmogorov–Smirnov test was used to determine the adherence of the data to the Gaussian curve. The paired *t*-test