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Original Article

Influence of bilevel positive airway pressure on autonomic tone in hospitalized patients with decompensated heart failure

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Abstract. [Purpose] This study evaluated the effect of Bilevel Positive Airway (BiPAP) on the autonomic control of heart rate, assessed by heart rate variability (HRV), in patients hospitalized with decompensated heart failure. [Subjects and Methods] This prospective cross-sectional study included 20 subjects (age: 69±8 years, 12 male, left ventricular ejection fraction: 36 ±8%) diagnosed with heart failure who were admitted to a semi-intensive care unit with acute decompensation. Date was collected for HRV analysis during: 10 minutes spontaneous breathing in the resting supine position; 30 minutes breathing with BiPAP application (inspiratory pressure = 20 cmH$_2$O and expiratory pressure = 10 cmH$_2$O); and 10 minutes immediately after removal of BiPAP, during the return to spontaneous breathing. [Results] Significantly higher values for indices representative of increased parasympathetic activity were found in the time and frequency domains as well as in nonlinear Poincaré analysis during and after BiPAP in comparison to baseline. Linear HRV analysis: standard deviation of the average of all R-R intervals in milliseconds = 30.99±4.4 pre, 40.3±6.2 during, and 53.3±12.5 post BiPAP. Non-linear HRV analysis: standard deviations parallel in milliseconds = 8.31±4.3 pre, 12.9±5.8 during, and 22.8 ±6.3 post BiPAP. [Conclusion] The present findings demonstrate that BiPAP enhances vagal tone in patients with heart failure, which is beneficial for patients suffering from acute decompensation.
Key words: Noninvasive ventilation, Cardiac heart failure, Autonomic nervous system

INTRODUCTION

Heart failure is a complex, multisystem condition resulting in inadequate blood supply to meet the metabolic needs of tissues in the presence of normal venous return, or can only meet such needs with higher than normal filling pressures[1].The hemodynamic changes commonly found in heart failure involve inadequate cardiac output and an increase in both pulmonary

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and systemic venous pressure. Compromised cardiac output is apparent with varying degrees during exercise and, in its most severe form, is observed in the resting state[1]. Such changes in heart function generally lead to multiple hospitalizations, often with the need for mechanical ventilation.

At some point after the initial insult of compromised cardiac function in heart failure, a chronic heightened activation of the sympathetic nervous system occurs, leading to an imbalance in autonomic tone, a shift away from vagal activity, that further contributes to and accelerates cardiac dysfunction[2–4]. On the other hand, variations in alveolar and intrathoracic pressures as well as the activity of pulmonary receptors through the use of positive airway pressure modulate autonomic tone, specifically increasing vagal activity[5]. Increased non-cholinergic and non-adrenergic vagal activation induced by positive airway pressure is also associated with coronary vasodilatation through activation of vasoactive intestinal peptides[6, 7]. Lastly, the magnitude of positive airway pressure used influences the degree to which hemodynamics, efferent vagal activity and heart rate are impacted[8, 9].

In the literature, Parati and Esler[3] reported continuous positive airway pressure (CPAP) is a viable non pharmacological option for sympathetic inhibition. Yoshida et al.[10] suggest that the administration of CPAP combined with support pressure is more effective than CPAP alone at achieving an increase in the cardiac index and this improvement may be related to a combination of both neural and mechanical effects, such as a reduction in ventricular preload.

Given the obvious effects heart failure has on autonomic balance in HF, research examining the ability of positive airway pressure to improve this physiologic abnormality would be beneficial. Thus, the aim of the present study was to investigate autonomic modulation in hospitalized patients with heart failure submitted to acute treatment with bilevel positive airway pressure (BiPAP) during noninvasive ventilation. Our hypothesis was that the administration of BiPAP during noninvasive ventilation would result in a beneficial autonomic response in hospitalized patients with heart failure.

SUBJECTS AND METHODS

A prospective, cross-sectional study was carried out at the semi-intensive care unit of the Albert Einstein Israelita Hospital following approval from the human research ethics committee of the Albert Einstein Teaching and Research Institute (Sao Paulo, Brazil) under process nº 263/2011. All patients received information regarding the objectives of the study and gave their consent to participation by signing a statement of informed consent.

The patients were admitted to the hospital after a decompression. All were invited to participate in the protocol, but only those who consented participated

The sample was selected consecutively with the following inclusion criteria: age 18 years or older; clinical diagnosis of decompensated heart failure; use of noninvasive ventilation; a left ventricular ejection fraction less than 50% confirmed by echocardiography; and New York Heart Association classification I-IV. The following were the exclusion criteria: coexisting chronic respiratory disease; unstable angina; second or third degree atrioventricular block; supraventricular tachycardia, frequent premature ventricular contractions, atrial flutter or atrial fibrillation; bronchodilator therapy; and incapacity or refusal to perform the proposed protocol. After applying the inclusion and exclusion criteria, 20 subjects were included in the study.

Data collection of subject characteristics involved review of clinical history, and confirmation of previous medical diagnoses and medication use. Heart rate (HR) and the interval between consecutive heart beats (R-R interval) were determined at rest with and without the use of BiPAP during noninvasive ventilation.

A Polar RS 800CX monitor (Polar Electro Oy, Kempele, Finland) was used for the acquisition of HR and the R-R interval data for the subsequent analysis of heart rate variability (HRV). The strap (Polar Wearlink Heart Rate Transmitter) was attached to the patient's thorax over the lower third of the sternum. Data recordings were always performed in the afternoon with the patient conscious within 72 hours of admission to hospital in a room with the temperature controlled at 21° C. No patient had ingested any food or liquid prior to the procedure. Data collection began after HR had stabilized in the resting state.

The data recording began during spontaneous breathing for ten minutes and continued while with the patient at rest received BiPAP (Vision, Respironics/Philiphs, USA) in spontaneous/time mode, with positive inspiratory airway pressure of 20 cmH$_2$O[11] and positive expiratory airway pressure of 10 cmH$_2$O[12] for 30 minutes using a full face mask (Respironics). After the withdrawal of BiPAP, HR and iRR were determined for an additional 10 minutes, a total of 50 minutes of recording. During the evaluation, peripheral oxygen saturation (SpO$_2$), blood pressure and respiratory rate (Vf) were displayed on a monitor (IntelliVue MP70 Anesthesia, Philips Medizinsysteme, Boeblingen, Germany) and recorded.

The HR and R-R interval data were imported by the Polar Precision Performance program and exported as *txt* files. All ectopic heartbeats or artifacts from signal movements were analyzed through a visual inspection of the computer screen. R-R intervals that differed by ± 20 bpm from the mean of the period analyzed were manually excluded. Only segments with more than 90% pure sinus beats were included in the final analysis. At least 256 R-R intervals from the most stable sessions were selected and analyzed with the aid of the Kubios HRV Analysis Program 2.0 for Windows (Biomedical Signal and Medical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland)[13]

HRV was analyzed using three linear measures in the time and frequency domains. Mean HR and mean R-R interval data, standard deviation of the mean of all R-R intervals (STDRR) and the square root of the sum of the square of the differences between R-R intervals divided by the number of R-R intervals in a determined time minus 1 (RMSSD) were computed as

measures of the time domain. HRV was calculated in the frequency domain using fast Fourier transforns, with evaluations of the low frequency (LF) and high frequency (HF) indices in normalized units and the LF/HF ratio[14].

Nonlinear measures were also used for the detrended fluctuation analysis (DFA) as an exponent of the short-term scale ($\leq$ 11 beats; DFAα1) in a set of R-R data. A Poincaré graph was used to obtain the standard deviations perpendicular (SD1) and parallel (SD2) to the identity line of the R-R intervals[14–16].

Data analysis was performed using the Minitab 14 statistical package. The sample size (20 patients) was calculated to yield an 80% power and $\alpha = 0.05$, using the LF component of autonomic activity as the outcome[17]. The Shapiro-Wilk test was used to examine the parametric distribution of baseline characteristics, which were expressed as mean and standard deviation values. ANOVA with Tukey's post hoc test was used for comparisons between different evaluations, and significance was accepted for values of $p < 0.05$.

RESULTS

Twenty-six patients were received evaluations, and six of them were excluded (3 exhibited high-response arterial fibrillation, 2 exhibited claustrophobia and 1 did not complete the study). Table 1 displays the demographic, anthropometric and clinical data of the sample (n = 20).

Table 2 displays the physiological variables (Vf, blood pressure and SpO$_2$) evaluated before (baseline), during and after

Table 1. Demographic, anthropometric and clinical characteristics

Variable	IC (n = 20)
Anthropometric characteristics	
Age (years)	69.0 ± 8.0
Height (m)	1.65 ± 0.8
Body mass (kg)	67.0 ± 8.0
BMI (kg/m²)	24.5 ± 0.6
Class NYHA *	
I	20%
II	15%
III	40%
IV	25%
Echocardiography	
Ejection fraction of the left ventricle (%)	36 ± 7
Cause of heart failure	
Dilated cardiomyopathy	60%
Idiopathic dilated cardiomyopathy	40%
Medication - Patients (%)	
Beta-blocker	17 (85%)
Digoxin	7 (35%)
Nitrato	3 (15%)
Angiotensin-converting enzyme inhibitors	17 (85%)
Furosemide	7 (35%)
Acetylsalicylic acid	3 (15%)

Table 2. Physiological parameters obtained before, during and after application of BiPAP for patients with HF

	IC (n = 20)		
	Pre BiPAP	During BiPAP	Post BiPAP
RR (rpm)	16±4	14±5	13±6
SBP (mmHg)	145±14	138±16*	125±13[#¥]
SpO$_2$ (%)	91±3	94±2*	96±3[#¥]

RR: Respiratory rate, SBP: systolic blood pressure, SpO$_2$: peripheral oxygen saturation, BiPAP: Bilevel positive airway pressure
*significant (p<0.05) difference between pre and during BiPAP; #significant (p<0.05) difference between during and after BiPAP; ¥significant (p<0.05) difference between pre and post BiPAP

the administration of BiPAP. No significant differences in Vf were found among the conditions. A significant reduction in systolic blood pressure was found during and after noninvasive ventilation in comparison to the baseline evaluation. Moreover, an increase in SpO_2 was found during and after BiPAP in comparison with the baseline evaluation.

Table 3 displays autonomic modulation based on linear and nonlinear indices of HRV obtained at rest before, during and after BiPAP. Significantly higher indices representative of parasympathetic activity were found in the time and frequency domains as well as in the nonlinear Poincaré analysis (RMSSD, HF, SD1) during and after BiPAP in comparison with the baseline evaluation.

DISCUSSION

The present study assessed the effects of BiPAP on autonomic tone in patients hospitalized secondary to decompensated heart failure. The major finding was that acute treatment with BiPAP resulted in a favorable autonomic adjustment in these patients, increasing vagal activation, as demonstrated by the higher HRV indices related to parasympathetic activity (RMSSD, HF and SD1). These findings have important clinical implications given prior evidence indicates increased parasympathetic tone protects the heart from arrhythmias induced by an electrophysiological imbalance[18]. Certainly this treatment goal is relevant and of importance for patients with decompensated heart failure.

The lowest LF and LF/HF ratio during the brief BiPAP intervention in comparison to spontaneous breathing also demonstrated the positive effect of this noninvasive ventilation approach, as these indices are related to sympathetic activity, which is associated with cardiac electrical instability, platelet aggregation, coronary vasoconstriction and greater stress on the wall of the myocardium[19, 20]. As HF and RMSSD are considered markers of vagal modulation and LF is associated with sympathetic activity[21], an increase in sympathetic activity and reduction in parasympathetic activity are associated with arrhythmia and an increased risk of death[2, 21, 22]. Thus, the present findings demonstrate the benefits of BiPAP in patients with decompensated heart failure regarding these aspects.

The overall improvement in HRV (STDRR, SD2) after certain interventions has been associated with a reduction in cardiovascular risk[20]. Consequently, it is reasonable to assume that the administration of BiPAP promoted the stimulation of vagal tone. It should be noted that only the acute response was evaluated in the present study and the longer-term effects are unknown. Future studies should examine the impact of a longer BiPAP intervention on the maintenance of autonomic tone.

Low nonlinear indices of HRV (denominated DFAα) are associated with a greater likelihood of adverse cardiac events and death. Ksela et al.[23] found a greater frequency of arrhythmia in patients with a lower DFAα. In the present study, the increase in DFAα during BiPAP suggests a reduction in the risk of developing arrhythmia.

Autonomic activity in the heart (as evaluated by HRV) is depressed in patients with heart failure[2, 24], and is associated with a greater mortality rate among such patients. Indeed, depressed autonomic activity is a predictor of hemodynamic impairment, death due to progressive cardiac dysfunction heart failure and sudden death[25–28]. Thus, positive airway pressure is commonly used during the hospitalization of patients with heart failure and the present findings demonstrate that this

Table 3. Linear and nonlinear heart rate variability indices evaluated before, during and after application of BiPAP in patients with HF

IC (n = 20)			
	Pre BiPAP	During BiPAP	Post BiPAP
Linear HRV			
Mean RR (ms)	782.6±115.4	814.6±116.6	790.1±112.0
STDRR (ms)	30.99±4.4	40.3±6.2*	53.3±12.5#¥
Mean HR (1/min)	71.4±11.6	77.2±11.7*	86.5±13.2#¥
rMSSD (ms)	14.9±10.2	17.2±2.9*	23.5±5.7#¥
LFun	74.9±10.4	64.2±12.9	73.9±9.28#
HFun	25.1±10.2	35.8±11.8*	27.4±9.8
LF/HF ratio	3.9±2.7	2.2±1.5*	3.2±1.4
HRV Nonlinear			
SD1 (ms)	8.31±4.3	12.9±5.8*	22.8±6.3#¥
SD2 (ms)	50.6±7.6	47.7±10.0*	70.3±17.7#
DFAα$_1$	0.92±0.5	1.14±0.5*	0.79±0.31#

Data presented as mean ± SD. BiPAP: Bilevel positive airway pressure, RR: RR interval, STDSS: standard deviation of the average of all R-Ri, HR: heart rate, rMSSD: square root of the sum of the squared differences between RR, LF: low frequency, HF: high frequency, SD: standard deviation, DFA: analysis of fluctuations purified trend
*significant (p<0.05) difference between pre and during BiPAP; #significant (p<0.05) difference between during and after BiPAP; ¥significant (p<0.05) difference between pre and post BiPAP

benefit goes beyond the hemodynamic response to also include a favorable neural response of the autonomic nervous system. These findings are in agreement with data described by Panatoni et al.[29] in a study involving hospitalized patients following re-vascularization surgery of the myocardium, in which CPAP also positively affected autonomic heart function.

It is necessary to understand the connections of the autonomic nervous system, respiratory system and heart to offer adequate care for patients with heart failure. Moreover, it is of the utmost importance to know that these systems exert effects on one another. Thus, in order to optimize treatment and outcomes, all of the aforementioned systems should be targeted with proven effective interventions.

In terms of hemodynamics, BiPAP has proved to be better than CPAP for patients with heart failure. Haruki et al.[30] evaluated the administration of adaptive servoventilation for patients with heart failure and found a reduction in post-load, increases in cardiac output and systolic volume as well as a beneficial effect on ventricular remodeling and left ventricular function, along with a reduction in mitral valve regurgitation. While no evaluation was performed in the present study of the autonomic response in CPAP mode without support pressure, a previous study by our research group evaluated this aspect and found a better autonomic response with CPAP of 10 cmH$_2$O.

Autonomic dysfunction with an increase in sympathetic activity and a reduction in parasympathetic activity has been reported in patients with heart failure. This dysfunction is associated with arrhythmia and an increased risk of adverse cardiovascular events and death[31]. Noninvasive ventilation has been widely used as an effective support during convalescence in this population because it improves ventilatory and hemodynamic variables as well as autonomic balance. The findings of the present study demonstrate that BiPAP also promotes different autonomic responses. Further studies are needed to evaluate the autonomic balance elicited by the chronic use of noninvasive ventilation in these patients.

The main limitation of this study was the lack of a control group receiving CPAP without support pressure. This was not approved by the ethics committee due to the fact that the hemodynamic response of CPAP is individualized for each patient with heart failure. Another limitation of the present study was the non-standardization of the use of medications, as it was not possible to intervene in the therapeutic approach prescribed by the medical team.

The present findings demonstrate that BiPAP results in beneficial autonomic responses due to vagal activation in patients with heart failure who were hospitalized for acute decompensation.

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