The acute effect of bi-level positive airway pressure on heart rate variability in chronic obstructive pulmonary disease patients with hypercapnic respiratory failure

Hiperkapnik solunum yetmezliği olan kronik obstrüktif akciğer hastalarında noninvazif mekanik ventilasyonun kalp hızı değişkenliği üzerine olan akut etkisi

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ABSTRACT

Objective: Non-invasive mechanical ventilation (NIMV) has the potential to improve sympathovagal control of heart rate. The aim of this study was to investigate the acute effects of NIMV on heart rate variability (HRV) in chronic obstructive pulmonary disease (COPD) patients with hypercapnic respiratory failure (HRF).

Methods: In this prospective study 28 COPD patients (64±10 years) with HRF underwent electrocardiographic Holter monitorization. Both time domain (TD) and frequency domain (FD) means of HRV analysis were measured for two hours before and during NIMV application. For the TD, mean-RR, SDNN, SDANN, SDNN index, RMSSD, pNN50 and HRV triangular index were measured. For FD, high frequency (HF) and low frequency (LF) were detected. To compare HRV parameters before and during bi-level positive airway pressure (BiPAP) application; paired sample t test was used for normally distributed variables and Wilcoxon signed rank test was used for the variables that were not normally distributed. Pearson correlation test was used to analyze the correlation between HRV and blood gas parameters during BiPAP application.

Results: High frequency power of HRV (39 (18-65) ms^2 vs. 28 (12-50) ms^2, $p<0.05$), HRV triangular index (9 (3-17) units vs. 6 (2-13) units, $p<0.05$) and pNN50 (59% (13-110) vs. 42% (5-84), $p<0.05$), were higher during NIMV than before noninvasive mechanical ventilation.

Conclusions: We think that NIMV may improve heart rate variability indices of parasympathetic modulation of heart rate in COPD cases with HRF and decrease arrhythmic potential. *(Anadolu Kardiyol Derg 2008; 8: 426-30)*

Key words: Heart rate variability, bi-level positive airway pressure, hypercapnia

ÖZET

Amaç: Noninvazif mekanik ventilasyonun (NIMV) kalp hızının sempatovagal kontrolünü iyileştirici etkisi mevcuttur. Bu çalışmanın amacı hiperkapnik solunum yetmezliği olan kronik obstrüktif akciğer hastalığı (KOAH) olanlarda NIMV'nin kalp hızı değişkenliği (HRV) üzerine olan akut etkisini araştırmaktır.

Yöntemler: Bu prospektif çalışmada hiperkapnik solunum yetmezliği olan 28 (64±10 yaş) KOAH'lı hastaya elektrokardiyografik Holter monitorizasyonu yapıldı. Iki seviyeli pozitif havayolu basıncı (BiPAP) uygulamasından 2 saat önce ve uygulama sırasında zaman-alan (TD) ve frekans-alan (FD) HRV analizleri yapıldı. Zaman-alan için, ortalama-RR, SDNN, SDANN, SDNN indeks, RMSSD, pNN50 ve HRV triangüler indeks hesaplandı. Frekans-alan için, yüksek frekans (HF) ve düşük frekans (LF) kuvvetleri hesaplandı. İki seviyeli pozitif havayolu basıncı uygulaması öncesi ve sırasındaki HRV parametrelerinden normal dağılıma uyanlar eşleştirilmiş t test ile uymayanlar ise Wilcoxon işaretli sıralar testi ile karşılaştırıldı. İki seviyeli pozitif havayolu basıncı sırasındaki HRV parametreleri ile kan gazı parametreleri arasındaki ilişki ise Pearson korelasyon test kullanılarak analiz edildi.

Bulgular: Yüksek frekans, HRV triangüler indeks ve pNN50 uygulama sırasında NIMV öncesine göre daha yüksekti (sırasıyla, 39 (18-65) ms^2 karşı 28 (12-50) ms^2, $p<0.05$; 9 (3-17) karşı 6 (2-13), $p<0.05$; %59 (13-110) karşı %42 (5-84), $p<0.05$).

Sonuç: Hiperkapnik solunum yetmezlikli KOAH hastalarında NIMV'nin kalp atım hızı değişkenliği parasempatik göstergelerini iyileştirerek aritmik potansiyeli azaltacağını düşünmekteyiz. *(Anadolu Kardiyol Derg 2008; 8: 426-30)*

Anahtar kelimeler: Kalp atım hızı değişkenliği, iki seviyeli pozitif havayolu basıncı, hiperkapni

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Introduction

Chronic obstructive pulmonary disease (COPD) refers to a group of related disorders characterized by progressive, nonreversible airflow obstruction (1). Supraventricular and ventricular rhythm disorders are common in COPD. Presence of ventricular arrhythmia in patients with COPD is reported to be associated with high mortality, particularly during hospitalization (2). There are reports of increased risk of sudden death in this group of patients. Ambulatory electrocardiographic (ECG) monitoring in patients with COPD has demonstrated that such patients have frequent abnormalities of cardiac rate and rhythm (3). Impaired autonomic regulation of heart rate was observed in both hypoxemic and normoxemic patients with COPD. Moreover, sympathetic activation and parasympathetic (PS) withdrawal seem to be associated with worse prognosis in such patients (4, 5). Non-invasive mechanic ventilation (NIMV) in the pulmonary intensive care unit (ICU) has been shown to reduce the need for intubation and the in-hospital mortality associated with severe exacerbations of COPD (6). Variations in intrathoracic pressure generated by different ventilator weaning modes may significantly affect intrathoracic hemodynamics and cardiovascular stability (7). In addition, a study demonstrated that positive pressure ventilation acutely increases baroreflex sensitivity for heart rate in association with reductions in systemic blood pressure in patients with obstructive sleep apnea and heart failure (8). Heart rate variability (HRV), which is a noninvasive diagnostic method, has been used to determine risk stratification in cardiac and noncardiac diseases (9, 10). Non-invasive mechanic ventilation has the potential to improve sympathovagal control of heart rate in acute cardiogenic pulmonary edema (11). However, there is few data about the effect of NIMV on parasympathetic control of heart rate, which is a parameter of cardiac autonomic function, in patients with acute COPD exacerbation. The aim of this study was to investigate the acute effects of bi-level positive airway pressure (BiPAP) on cardiac autonomic function in COPD patients with hypercapnic respiratory failure (HRF).

Methods

Subjects and study design

This prospective study was performed in the department of pulmonary diseases and intensive care unit (ICU) between November 2005 and April 2006. Twenty-eight patients (mean age - 64±10 years) with HRF in acute exacerbations of COPD were studied. All patients had COPD according to the American Thoracic Society/European Respiratory Society guidelines (1). The subjects with diabetes mellitus, atrial fibrillation, systemic arterial hypertension, hemodynamic instability, and coronary artery disease, neurological or any other systemic disorder that might influence autonomic function were excluded from the study. All patients gave informed consent to participate in the study, which was approved by the hospital ethical committee.

Acute HRF was defined by arterial blood gas criteria (partial pressure of carbon dioxide: $PaCO_2$ >45 mmHg (6kPa), and pH< 7.35). Characteristics of patients such as age, gender, Acute Physiology and Chronic Health Evaluation II Score (APACHE II) (12) and mortality rate were recorded. Complete blood count and routine biochemical analysis were done at ICU admission. Before and at the second hour of NIMV application arterial blood gas parameters such as $PaCO_2$, PaO_2 and pH were also measured. None of the study patients was receiving autonomically active medications other than inhaled beta-agonist, antibiotic, intravenous aminophylline, steroid, subcutaneous low molecular-weight heparin and/or anticholinergic agents. Both before and during BiPAP application patients were receiving intravenous 6 mg/kg/day aminophylline infusion in constant dose. We used the criteria for indications for NIMV in HRF. These criteria were: 1-exacerbation of COPD, 2- respiratory acidosis (pH=7.25-7.35), and 3- a respiratory rate greater than 23 breaths per minute (13). Non-invasive mechanic ventilation was administered using BiPAP ventilation via the BiPAP Vision ventilator (Respironics, Murrysville, Pennsylvania, USA). This device is capable of providing independently adjustable inspiratory and expiratory positive airway pressure. BiPAP was administered at a level of 5 cm H_2O of expiratory positive airway pressure and 15 cm H_2O of inspiratory positive airway pressure, in a spontaneous/time mode. Heart rate variability analysis was measured for two hours before and during NIMV. Throughout the Holter recording the cases were awake.

HRV analysis

The recordings were replayed through a Pathfinder arrhythmia analyzer (Reynolds Medical Ltd). Both time- and frequency-domain analyses were performed for two hours before and during BiPAP. For the time-domain, mean N-N interval (mean-RR), the standard deviation of all NN intervals (SDNN), the standard deviation of the average NN intervals calculated over 5-minute periods throughout the recording (SDANN), the mean of the standard deviation of the 5-minute NN intervals over the entire recording (SDNN index), the root mean square of the difference between successive NN intervals (RMSSD), the proportion of adjacent normal NN intervals differing by >50 ms (pNN50), and total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms (=1/128 seconds) (HRV triangular index: measure expressing overall HRV) were calculated. For the frequency-domain analysis, power spectral analysis based on the fast Fourier transformation algorithm was used. Two components of power spectrum were computed following bandwidths: high frequency (HF) (0.15-0.4 Hz) and low frequency (LF) (0.04-0.15 Hz). The LF/HF ratio was also calculated.

Statistical analysis

Statistical analysis was performed using SPSS for Windows 10.0 (SPSS Inc., Chicago, Illinois, USA). Normally distributed data are presented as mean±standard deviation, and data that were not normally distributed are presented as median (Min-Max). To compare HRV parameters before and during BiPAP application; paired sample t test was used for normally distributed variables and Wilcoxon signed rank test was used for the variables that were not normally distributed. Pearson correlation test was used to analyze the correlation between HRV and blood gas parameters during BiPAP application. A p value <0.05 was considered as statistically significant.

Results

Demographic characteristics of the patients, biochemical parameters, arterial blood pressure and blood counts are displayed in Table 1. The HRV parameters before BiPAP and during BiPAP are shown in Table 2. There were significant differences between before BiPAP and during BiPAP with respect to HF, pNN50 and HRV triangular index (p=0.039, p=0.035, p=0.042, respectively). There were no significant differences in mean RR, SDNN, SDNN index, SDANN, RMSSD, LF and LF/HF (for all p>0.05) before BiPAP and during BiPAP. Arterial blood gases before BiPAP and during BiPAP are shown in Table 2. There were significant differences between before BiPAP and during BiPAP with respect to $PaCO_2$ (p=0.020) and PaO_2 (p=0.001). There were significant differences in systolic and diastolic arterial blood pressure (p=0.015, p=0.020, respectively) before BiPAP and during BiPAP.

Table 3 shows correlation analysis data between HRV and blood gas parameters. There was no correlation between time- and frequency-domain HRV parameters and blood gas levels obtained during BiPAP application (p>0.05 for all).

Table 1. Demographic and laboratory characteristics of patients

Variables	Mean±SD
Age, years	64±10
Length of ICU stay, days	9.3±3.0
APACHE II, score	16.9±4.0
Body temperature, °C	36.5±0.4
Respiratory rate, /minutes	26±8
Pulse /minutes	102±18
Blood pressure, systolic, mmHg	127±14
Blood pressure, diastolic, mmHg	76±8
Leukocyte, /mm^3	13072±5475
Hematocrit, %	41±7
Creatinine, mg/dL	1.26±0.6
K+, mEq/L	4.2±0.6
Albumin, g/dL	3.4±0.6

ICU - intensive care unit

Discussion

In the present study, we investigated the acute effects of BiPAP on cardiac autonomic function in COPD patients with HRF. We found that BiPAP application increased parasympathetic activity in these patients. These findings suggest that in patients with HRF in acute exacerbations of COPD may benefit from BiPAP application in addition to standard therapy.

The autonomic system controls physiological processes such as regulation of the airway smooth muscle tone, secretion of mucus from submucosal glands, fluid transport through the airway epithelium, capillary permeability and release of mediators

Tablo 2. Comparison of arterial blood gases, arterial blood pressure and HRV parameters before BiPAP and during BiPAP

Variables	Before BiPAP	During BiPAP	p
pH*	7.26±0.90 (7.17-7.37)	7.29±0.40 (7.23-7.35)	0.107
$PaCO_2$, mmHg	67 (30-95)	60 (34-82)	0.020
PaO_2, mmHg	61 (38-95)	75 (43-105)	0.001
Heart rate /min	102 (70-132)	98 (60-123)	0.262
Respiratory rate/min	25 (22-34)	24 (18-29)	0.06
Blood pressure, systolic, mmHg*	127±14 (110-145)	116±11 (105-125)	0.015
Blood pressure, diastolic, mmHg*	76±8 (65-87)	69±7 (63-77)	0.020
Mean RR, ms	610 (460-715)	603 (480-750)	0.164
SDNN, ms	50 (15-92)	55 (18-96)	0.948
SDNN index, ms	37 (10-69)	42 (8-75)	0.463
SDANN, ms	29 (8-53)	31 (17-48)	0.437
RMSSD, ms	47 (3-95)	56 (12-104)	0.140
pNN50, %	42 (5-84)	59 (13-110)	0.035
HRV triangular index, units	6 (2-13)	9 (3-17)	0.042
LF, ms^2	26 (8-55)	29 (13-60)	0.501
HF, ms^2	28 (12-50)	39 (18-65)	0.039
LF/HF ratio	0.92 (0.4-1.3)	0.74 (0.42-1.07)	0.252

Paired Sample t test* and Wilcoxon Signed Rank test
Data are presented as Mean±SD* and Median (Min-Max) values
BiPAP - bi-level positive airway pressure, HF - high frequency power, HRV - heart rate variability, LF - low frequency power, $PaCO_2$ - partial pressure of carbon dioxide in the arterial blood, PaO_2 - partial pressure of oxygen in the arterial blood, pNN50 - proportion of adjacent normal-to-normal (NN) intervals differing by >50 ms, RMSSD - root mean square of the difference between successive NN intervals, SDANN - standard deviation of the average NN intervals calculated over 5-minute periods throughout the recording, SDNN - standard deviation of all NN intervals, SDNN index - mean of the standard deviation of the 5-minute NN intervals over the entire recording

Table 3. Correlation between HRV and blood gas parameters during BiPAP application

	r	p
pNN50-$PaCO_2$	0.32	0.813
pNN50-PaO_2	-0.17	0.183
pNN50-pH	-0.08	0.207
HRV triangular index- $PaCO_2$	0.21	0.750
HRV triangular index- PaO_2	0.41	0.756
HRV triangular index- pH	-0.31	0.390
HF- $PaCO_2$	0.21	0.116
HF- PaO_2	-0.18	0.687
HF- pH	0.03	0.725

Pearson Correlation test
BiPAP - bi-level positive airway pressure, HF - high frequency power, HRV - heart rate variability, $PaCO_2$ - partial pressure of carbon dioxide in the arterial blood, PaO_2 - partial pressure of oxygen in the arterial blood, pNN50 - proportion of adjacent normal-to-normal (NN) intervals differing by >50 ms

from inflammatory cells (14). Pathogenetic mechanisms of autonomic dysfunction in patients with COPD have not yet been clearly understood. Patients with autonomic dysfunction have a high mortality and incidence of sudden death occurring under conditions of stress and hypoxemia (3). Decreased HRV, which represents autonomic dysfunction is associated with increased mortality and morbidity with various forms of heart disease and COPD (15). The decreased HRV in patients with COPD, and further decrease in HRV in patients with a change in their clinical status, suggests that HRV will be important measure of overall physiologic and functional status of individuals with COPD. In a study by Tuğ et al., parasympathetic dysfunction was found in 70% of patients with AD in COPD (14). These findings indicate that the frequency of parasympathetic dysfunction is higher than sympathetic dysfunction in COPD patients.

In our study HF, pNN50 and HRV triangular index were increased during NIMV in patients with COPD and respiratory failure. Meduri et al. (16) first described the use of NIMV in patients with acute respiratory failure. Keenann et al (17) reported that within the first hours of NIMV application, severity of dyspnea is reduced in association with improvement of blood gases and pH. Consistent with other studies utilizing continuous positive airway pressure or BiPAP in which an increase in cardiac output and an improvement in ventricular contractility were also found in patients with acute respiratory failure (18, 19). The mechanism of improvement in cardiac function with the placement of BiPAP seems unclear. One of the mechanisms may be improvement in hypoxia, hypercapnia and pH. However, we detected no correlation between blood gas and HRV parameters. Summers et al. (20) reported that little or no change was observed in heart rate while using BiPAP indicating a stable sympathetic output both COPD patients and controls. Even noninvasive elevations in airway pressure would be expected to increase intrathoracic pressures and reduce venous return (19). This effect could be offset by a reduction in pulmonary vascular resistance caused by the improved oxygenation of the newly opened alveoli (19, 20).

Several authors have reported the harmful effect of increased sympathetic activity and the protective role of vagal activity in patients with cardiovascular disease (21). Treatment modalities decreasing the sympathetic activity and /or increasing parasympathetic activity by correcting the autonomic control of cardiovascular system have been suggested to lower cardiac death (22). Although there are negative studies (23), recent studies were reported supporting that NIMV improves HRV. Sin et al (24) reported that NIMV applied nocturnally over 3 months may improve HRV, reduce circulating natriuretic peptide levels, and enhance the functional performance of patients with severe but stable COPD. In another study Skyba et al. reported that NIMV application in patients with COPD exacerbations improved HRV and hemodynamics parameters (25). Our results are consistent with these studies, and we found parasympathetic increase after BiPAP application. Another study performed in COPD patients revealed that BIPAP application increased sympathetic activity (26). Even though the cause of this difference is not well known, enrollment of stable COPD patients in contrast to our study might be the reason.

Study limitations

In this study, we analyzed acute effect of BiPAP on HRV parameters. To determine the direct effect of BiPAP on arrhythmic event and mortality long-term follow-up studies are needed.

Conclusion

Bi-level positive airway pressure acutely increases time- and frequency-domain indices of HRV, reflecting increase in parasympathetic modulation of heart rate. In other words, NIMV has the potential to improve parasympathetic control of heart rate in HRF with COPD and may decrease arrhythmic potential in COPD.

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