Cardiac Functions and All-Cause Mortality in Kyphoscoliosis Patients with Chronic Respiratory Failure Using Non-invasive Ventilation

Yusuf Karavelioğlu[1], Hekim Karapınar[2], Zuhal Karakurt[3], Göksel Açar[2], Özlem Yazıcıoğlu Moçin[3], Nalan Adıgüzel[3], Murat Yüksel[2], Gökay Güngör[3], Ali Metin Esen[2]

[1] Hitit University Medical School, Department of Cardiology, Çorum, Turkey
[2] Kartal Koşuyolu High Specialty Training and Research Hospital, Department of Cardiology, İstanbul, Turkey
[3] Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital, Respiratory Intensive Care Unit, İstanbul, Turkey

ABSTRACT

Introduction: We aimed to evaluate cardiac functions and mortality rate in kyphoscoliosis patients with chronic respiratory failure under long term non-invasive ventilation (NIV).

Patients and Methods: Kyphoscoliosis patients, who used NIV, were included in the study. Patients' characteristics and cardiovascular risk factors were recorded. Ambulatory rhythm monitoring and echocardiography were performed for all patients. Results were compared with 26 age-gender matched volunteers without dyspnea. Patients had been followed for five years.

Results: Twenty-three kyphoscoliosis patients (54 ± 13 years, 15 male) were included in the study. Hypertension and paroxysmal atrial fibrillation were more frequent in patients. Left ventricular systolic functions were normal but diastolic functions were worsened. Right ventricular sizes were normal but systolic and diastolic functions were worsened and the mean pulmonary artery pressure was higher in kyphoscoliosis patients. Four patients were died in follow up. Two of patients died due to severe hypoxia and two of them died due to sepsis. Clinical and laboratory properties including cardiovascular risk factors, echocardiographic examination were not different between the survived patients and dying ones.

Conclusion: Hypertension and arrhythmia are more frequent. The left ventricle is slightly affected but the right ventricle is severely affected and pulmonary pressure is increased in kyphoscoliosis. Cardiovascular functions do not predict mortality in kyphoscoliosis patients under long term NIV treatment.

Key Words: Kyphoscoliosis; mechanical ventilation; bi-level continucus positive airway pressure; cardiac function tests; pulmonary hypertension

İnvaziv Olmayan Ventilasyon Kullanan Kronik Solunum Yetersizlikli Kifoskolyoz Hastalarının Kardiyak Fonksiyonlarının ve Total Mortalitenin Değerlendirilmesi

ÖZET

Giriş: Biz bu çalışmada kronik solunum yetersizliği nedeniyle uzun dönem invaziv olmayan ventilasyon tedavisi alan kifoskolyoz hastalarında kardiyak fonksiyonlar ve mortalite oranları değerlendirmeyi amaçladık.

Hastalar ve Yöntem: İnvaziv olmayan ventilasyon kullanan kifoskolyoz hastaları bu çalışmaya alındı. Hasta özellikleri ve kardiyovasküler risk faktörleri kaydedildi. Tüm hastalara ambulatuvar ritim monitorizasyonu ve ekokardiografi yapıldı. Sonuçlar 26 yaş-cinsiyet ayarlanmış dispnesi olmayan gönüllüler ile karşılaştırıldı. Hastalar beş yıl süreyle takip edildi.

Bulgular: Yirmi üç kifoskolyoz hastası (54 ± 13 yaş, 15 erkek) çalışmaya alındı. Hipertansiyon ve paroksismal atrial fibrilasyon hasta grubunda daha sık izlendi. Sol ventrikül sistolik fonksiyonları normal iken diastolik fonsiyonları bozulmuş izlendi. Sağ ventrikül çapları normal iken sistolik/diyastolik fonksiyonları ortalama pulmoner arter basınçları kifoskolyoz hastalarında yüksek idi. Dört hasta takipte öldü. Ölümlerin ikisi ciddi hipoksemi nedeniyle diğer ikisi de sepsis nedeniyle gerçekleşti. Klinik, laboratuvar, ekokardiografi ve kardiyovasküler risk parametreler açısında ölenler ile hayatta kalanlar arasında fark izlenmedi.

Sonuç: Kifoskolyoz hastalarında hipertansiyon ve aritmi sık izlendi. Sol ventrikül hafif derecede fakat sağ ventrikül ciddi ölçüde etkilendiği ve pulmoner arter basınçlarının arttığı gözlendi. Uzun dönem invaziv olmayan ventilasyon tedavisi alan kifoskolyoz hastalarında kardiyovasküler fonksiyonlar mortaliteyi öngörmediği tespit edildi.

Anahtar Kelimeler: Kifoskolyoz; mekanik ventilasyon; iki-düzeyli pozitif hava yolu basıncı; kardiyak fonksiyon testleri; pulmoner hipertansiyon

Yazışma Adresi

Yusuf Karavelioğlu

E-posta: drcomtr@gmail.com
Geliş Tarihi: 03.12.2014
Kabul Tarihi: 25.12.2014

INTRODUCTION

Hypercapnia and hypoxemia due to hypoventilation develop in time especially during night in kyphoscoliosis patients with severe chest deformity. Nocturnal non-invasive ventilation (NIV) and oxygen therapy have positive effects on quality of life and cognitive functions in these patients[1-3].

Cardiovascular diseases in chronic respiratory failure patients are the most important causes of morbidity and mortality. Accompanying respiratory distress which is the major symptom of chronic respiratory failure, breathlessness, palpitation and fatigue are also frequently detected in cardiovascular diseases. In addition, pulmonary hypertension, right heart failure, and cor pulmonale can also occur in many pulmonary diseases. There are limited studies in English based literature about the frequency of cardiovascular risk factors and especially, the frequency of pulmonary hypertension and cor pulmonale in kyphoscoliosis patients[3]. Furthermore, there is no study performed with transthoracic echocardiography investigating cardiac functions of kyphoscoliosis patients.

We aimed to investigate cardiac functions and their relations with pulmonary functions and mortality in kyphoscoliosis patients with advanced chronic respiratory failure under long term NIV treatment.

PATIENTS and METHODS

Study Population and Protocol

This was a cross-sectional study of consecutive kyphoscoliosis patients with chronic respiratory failure who were followed-up by the outpatient clinic of the respiratory intensive care unit (RICU) and who, being under NIV treatment (Group 1), were included in the study. Consecutive patients were enrolled to the study during the period January to April of 2007. Control subjects (Group 2) were matched for gender and age. Long term NIV devices prescribing was made according to the following rules: patients with symptoms such as fatigue, dyspnea, morning headache and one of the partial carbon dioxide pressure ($PaCO_2$) > 45 mmHg and/or nocturnal oximetry demonstrating oxygen saturation (SpO_2) ≤ 88% for 5 consecutive minutes[1]. During this evaluation, all patients were stable and followed as outpatients. NIV devices of patients were recorded as follows: Applying bi-level positive airway pressure (BiPAP), breath-time assured BiPAP/ST and pressure support for spontaneous breath (BiPAP/S). Expiratory positive airway pressure (EPAP), inspiratory positive airway pressure (IPAP), and duration of use per day were recorded from device screen. If patients used the device 4 hours/day and 20 hours/week, compliance for device use was evaluated as good[1]. Presence of known cardiac risk factors, such as hyperlipidemia, hypertension, diabetes mellitus and smoking, were questioned. Functional capacity, spirometry and arterial blood gas (ABG) were detected under therapy. Cardiovascular examination was done, and 24-hours ambulatory rhythm monitoring and detailed echocardiography were performed. Patients with other causes of respiratory distress, such as COPD, obesity-hypoventilation syndrome, obstructive sleep apnea syndrome, diffuse interstitial lung disease and collagen vascular disease, were excluded from the study. In order to compare the respiratory and cardiac findings of the patients, 26 age-gender matched volunteers without dyspnea were selected as the control group (Group 2). Volunteers were recruited from consecutive gastroenterology outpatient clinic appliers. Kyphoscoliosis patients were followed up for five years for all-cause mortality. Informed consent was taken from all patients and an approval from the local ethical committee was obtained.

Echocardiography

Echocardiography examinations were performed using the Vivid 3 system equipped with 2.5-3.5 MHz transducer (GE, Horten, Norway) at the left decubitus position during end-expiratory apnea. The left atrium anterior-posterior diameter, diastolic diameters, and septal and posterior wall thickness of left ventricle (LV) were obtained by M-Mode images from parasternal long axis view. LV diastolic and systolic areas were obtained from the apical four and two chamber views, and ejection fraction was calculated by utilizing the modified Simpson's method. The right ventricular (RV) diastolic and systolic areas were measured from the apical four chamber view, and percent area changes were calculated as an index of RV systolic functions. Pulmonary artery systolic pressure was calculated by adding tricuspid regurgitation (TR), and if present, jet velocity to estimated right atrium (RA) pressure (4 x (TR velocity)2 + RA). Mean pulmonary artery pressure (PAP) was estimated by using pulmonary acceleration time (AT) measured by pulsed wave (PW) Doppler of the pulmonary artery in systole, whereby the mean PAP = 79-(0.45 x AT) and if AT < 120 ms, 90-(0.62 x AT) formula was used[4]. Cor pulmonale was described as RV enlargement and estimated systolic PAP≥ 40 mmHg[5,6].

LV and RV inflow early diastolic flow velocities (E) were obtained by PW Doppler, which involved a 2 mm sample volume placed at tips of atrioventricular valves from the apical four chamber view. The LV myocardial performance index (MPI) was calculated as the sum of the isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) divided by the ejection time (ET) [(IVRT + IVCT)/ET]. When time intervals were acquiring, the cursor was placed to the mid-line of the aortic and mitral valves from the apical five chambers view and sweep speed was adjusted to 50-100 mm/s[6].

Pulsed wave tissue Doppler imaging (TDI) was obtained by activating the machine's TDI function with gains adjusted to eliminate transvalvar flow velocities and minimize noise. In the apical 4-chamber view, a 5-10 mm sample volume was placed at the lateral side of the mitral and tricuspid annuli. Peak myocardial velocities of systole (S), early (e') and late (a') diastole together with the time intervals were measured at a sweep speed of 100 mm/s. Depth, gain and sector size were

optimized before obtaining images. In addition, special attention and care was given for the ultrasound beams to be perpendicular to the annuli. The TDI-derived MPI, as a global estimate of both systolic and diastolic function of the RV, was calculated as the sum of the isovolumetric contraction (IVCT) and relaxation (IVRT) time divided by the ejection time (ET).

Mitral and tricuspid annuli e'/a' ratios were determined as diastolic function indexes. LV filling pressure was estimated with transmitral early diastolic velocity to mitral annular early diastolic velocity (E/e') ratio. RV filling pressure was estimated with transtricuspid early diastolic velocity to tricuspid annular early diastolic velocity (E/e') ratio. The final values of all parameters were obtained after averaging over three cardiac cycles. All measurements were made by a single experienced observer, blinded to the patient's identity. Results were analyzed in the same session. Examinations were performed according to the established rules[7].

Spirometry, Artery Blood Gas Analysis and 24-hours Ambulatory Rhythm Monitoring

Spirometry was performed in all attendees according to established rules in the afternoon[8]. Spirometry was repeated three times, and best results were chosen. The volume of forced vital capacity (FVC), percentage of expected FVC (FVC%), volume of forced vital capacity in one second (FEV1) and FEV1/FVC ratio were detected. Radial arterial blood was withdrawn from all cases in room air during the afternoon for ABG. pH, partial carbon dioxide pressure ($PaCO_2$), partial oxygen pressure (PaO_2) and arterial oxygen saturation (SaO_2) were recorded from ABG. All subjects underwent 12-leads 24-hours ambulatory rhythm monitoring (Cardioscan Premier 12 Holter System, DMS, Stateline, NV, USA). Recordings were analysed with CardioScan-12 Holter ECG Systems (DMS software). Paroxysmal atrial fibrillation was defined by the following ECG criteria: mean ventricular rate >100 beats per minute, QRS morphology during tachycardia that was either normal or a functional bundle branch block, a grossly irregular ventricular rhythm, the absence of P waves or the presence of fibrillatory waves in the baseline when P waves had been recorded during periods of sinus rhythm, and episodic occurrence[9].

Statistical Analysis

Kyphoscioliosis and control subjects were compared by Mann Whitney U test for nonparametric continues variables, Student T test for parametric continues variables and Chi square test used for dichotomous variables. The relationship of pulmonary functions test results (arterial blood gasses values, spirometry tests results) and TTE findings were evaluated with Spearman's correlations test for nonparametric continues variables and Pearson's correlation test was used parametric continues variables. Correlations were tested for linearity by scatter plot graphics. And when linear correlation was not seen, correlations tested by Spearman's test. Median and interquartile range were used for continuous non-parametric variables; mean and standard deviation were used for continues parametric variables. Count and % were used for showing the nonparametric variables. For survival analysis, Kaplan Meier test was preferred due to limited mortality rate. Sophisticated regression analysis could not be implemented because of the limited mortality rate. P value < 0.05 was accepted as statistically significant.

RESULTS

Kyhoscoliosis and control subjects were similar according to age and gender. Group I consisted of 23 consecutive, stable (without exacerbation) kyphoscoliosis patients with long term (median 36.0, inter-quartile range 26.0 to 54.0 months) home nocturnal NIV. They were admitted to RICU at least once during their follow up due to acute respiratory failure (pH< 7.34 and $PaCO_2$> 45.0 mmHg). Two patients were tracheostomized at a previous RICU admission due to weaning failure and they had intermittent tracheostomized mechanical ventilation support. Ten patients (43.5%) used an NIV device with spontaneous mode (BiPAP/S), while 13 (56.5%) patients used an NIV device with time specific respiratory rate quarantined (BiPAP/ST). Mean ± standard deviation of EPAP and IPAP were 5.4 ± 0.8 mmHg and 17.1 ± 6.4 mmHg, respectively. Median daily device use was 8.0 (inter-quartile range 6.0 to 9.8) hours and 21 (91.3%) patients were compliant with device use (> 4 hours per day). Oxygen use was present in 19 (82.6%) cases. The functional class distribution of patients under NIV intervention were 18 (78.3%) in class II, 4 (17.4%) in class III and 1 (4.4%) in class IV. FVC, FVC%, FEV1, and FEV1% were significantly lower in group I; FEV1/FVC was similar in both groups. pH value in ABG was similar whereas $PaCO_2$, PaO_2, SO_2, HCO_3 and base deficit were significantly different in group I (Table 1).

Coronary risk factors were significantly higher in current and ex-smoker kyphoscoliosis patients. Hypertension was more frequent in group I but diabetes mellitus frequency was similar. Hyperlipidemia was absent in group I. Overt coronary artery disease was absent in both groups. All patients were in sinus rhythm but five patients (21.7%) have paroxysmal atrial fibrillation in group I; all subjects were in sinus rhythm in group II. Office and 24-hour heart rate was significantly higher in group I; both office systolic and diastolic pressures were similar in the groups. LV diastolic area, ejection fraction and RV diastolic area were not significantly different in both groups. RV area change was significantly lower in group I. There was no aortic valve insufficiency, but there was minimal mitral valve insufficiency in both groups (3 vs. 4 subjects, p= 0.77). Tricuspid valve insufficiency was present as ¼ degree in 8 patients of group I, while it was minimal in one subject and ¼ degree in two subjects of group II (p= 0.10). Mean pulmonary artery pressure, mitral lateral e'/a', LV E/e', tricuspid lateral e'/a', and RV E/e' were significantly different between the groups. The LV MPI index and RV MPI index

were not significantly different between the groups (Table 2).

Cor pulmonale was detected in four (17.4%) kyphoscoliosis patients. There was no significant difference in age and gender between kyphoscoliosis with cor pulmonale and kyphoscoliosis without cor pulmonale. In addition, there was no difference for duration of device follow up, RICU admission in the last year, spirometry values and ABG values other than PaO_2 among those patients. The demographic and clinical properties of patients with cor pulmonale compared to those without cor pulmonale were presented in Table 3. Frequency of tricuspid insufficiency, RV diastolic area, mean pulmonary artery pressure and RV MPI were higher, while fractional area change was detected as lower. Those were presented in Table 4.

Mean pulmonary artery pressure was found to be inversely correlated with PaO_2 in the correlation analysis (r= -0.54, p= 0.017). There was no correlation with $PaCO_2$, base deficit, FEV1 and FVC. Presence of cor pulmonale was inversely correlated with PaO_2 (r= -0.46, p= 0.036).

On follow up four (17.4%) patients died. One of them died 12 months later due to RICU associated sepsis, one of them died 16 months later due to severe hypoxemia, one of them died at 20 months later due to RICU associated sepsis and one them died 21 months later due to severe hypoxemia. Nineteen patients (82.6%) were survived and on follow up for five years. Long term survival functions curve was shown in Figure 1 by Kaplan Meier analysis.

There was no significant difference in respect to age and gender between patients who died and patients who survived. In addition, there was no difference for duration of device follow up, RICU admission in the last year, spirometry values

Table 1. Comparisons of groups for demographic, clinical, and laboratory properties

	Kyphoscoliosis (n: 23)	Control (n: 26)	P value
Age (years)	53.9 ± 13.2	52.4 ± 13.5	0.47
Male gender	15 (65.2%)	16 (61.5%)	0.78
NYHA Functional class: I/II/III/IV	0/18 (78.0%)/4 (17.0%)/1 (4.0%)	-	NA
NIV Device: (BPAP)/(BPAP/ST)/(BPAP/S)	8 (34.8%)/13 (56.2%)/2 (8.7%)	-	NA
NIV duration (months)*	36.0 (26.0-54.0)	-	NA
Daily NIV use (hours)*	8.0 (6.0-9.6)	-	NA
Device compliance	21.0 (91.3%)	-	NA
EPAP (cm H_2O)	5.4 ± 0.8	-	NA
IPAP (cm H_2O)	17.1 ± 6.4	-	NA
LTOT	19 (82.6%)	-	NA
Total hospitalization rates: 0/1/2/≥3 times	0/7 (30.4%) /1 (4.4%) /15 (65.2%)	-	NA
RICU hospitalization rates in last year: 0/1/2/≥3 times	6 (26.1%) /11 (47.8%) /3 (13.0%) /3 (13.0%)	-	NA
Previous intubation rates: 0/1/2/≥3 times	17 (73.9%)/4 (17.4%)/1 (4.4%)/1 (4.4%)	-	NA
Previous thoracic operation	2 (8.7%)	-	NA
Tracheostomized	2 (8.7%)	-	NA
pH	7.41 ± 0.10	7.38 ± 0.05	0.63
$PaCO_2$ (mmHg)	57.0 ± 11.3	36.1 ± 1.6	<0.001
PaO_2 (mmHg)	64.7 ± 10.6	82.2 ± 2.1	<0.001
HCO_3 (mmol/L)	32.1 ± 6.1	21.9 ± 1.2	<0.001
SaO_2 (%)	87.9 ± 8.0	93.8 ± 1.9	<0.001
FVC volume (mL)*	830.0 (775.0-1060.0)	3850.0 (2425.0-4525.0)	<0.001
FVC % predicted*	30.0 (24.8-40.3)	86.0 (80.0-100.0)	<0.001
FEV1 volume (mL)*	735.0 (649.5-895.0)	3400.0 (2100.0-4350.0)	<0.001
FEV1 % predicted*	34.0 (25.9-39.3)	85.5 (80.5-99.0)	<0.001
FEV1/FVC (%)*	84.0 (76.7-92.3)	88.5 (78.8-99.0)	0.95

NYHA: New York Heart Association, NA: Not applicable, NIV: Noninvasive ventilation, BiPAP: Bi-level positive airway pressure, BiPAP/ST: Breath-time assured BiPAP, BiPAP/S: Pressure support for spontaneous breath BiPAP, EPAP: Expiratory positive airway pressure, IPAP: Inspiratory positive airway pressure, LTOT: Long term oxygen therapy, RICU: Respiratory intensive care unit, $PaCO_2$: Partial arterial carbon dioxide pressure; SaO_2: arterial oxygen saturation, PaO_2: partial arterial oxygen pressure, FVC: Volume of Forced vital capacity, FVC%: percent of expected FVC, FEV1: Volume of Forced vital capacity in one second, FEV1%: percent of expected FEV1.
* Median (25-75 percentiles)

Table 2. Comparisons of groups for cardiovascular risk factors and findings

	Kyphoscoliosis (n: 23)	Control (n: 26)	P value
Smoking; ex smoker	13 (56.5%); 12 (92.3%)	6 (23.1%); 4(66.7%)	0.031
Hypertension (%)	11 (47.8%)	5 (19.2%)	0.032
Diabetes mellitus (%)	2 (8.7%)	2 (7.7%)	0.86
Hyperlipidemia (%)	0	5 (19.2%)	0.028
Office heart rate (per minute)	92.2 ± 12.4	78.1 ± 9.3	<0.001
Office systolic BP (mmHg)	131.7 ± 20.1	127.4 ± 18.1	0.13
Office diastolic BP (mmHg)	82.9 ± 13.4	79.1 ± 12.1	0.25
24 hours heart rate (per minute)	86.1 ± 14.2	70.1 ± 9.6	<0.001
Paroxysmal atrial fibrillation (%)	5 (21.7%)	0	<0.001
LV diastolic volume (mL)	77.5 ± 10.7	85.3 ± 12.3	0.35
LV ejection fraction (%)	65.3 ± 3.7	64.4 ± 3.3	0.69
RV end-diastolic area (cm^2)	24.7 ± 5.6	22.2 ± 2.4	0.06
RV fractional area change (%)	39.5 ± 9.0	45.9 ± 6.7	0.009
Mean PAP (mmHg)	27.2 ± 10.7	15.7 ± 6.6	<0.001
Mitral lateral e'/a'	0.94 ± 0.38	1.19 ± 0.47	0.008
LV E/e'	9.55 ± 4.26	6.93 ± 2.40	0.024
Tricuspid lateral e'/a'	0.72 ± 0.31	1.0 ± 0.33	0.005
RV E/e'	7.3 ± 4.2	5.1 ± 1.4	0.04
LV MPI index	0.59 ± 0.19	0.54 ± 0.16	0.23
RV MPI index	0.58 ± 0.20	0.50 ± 0.18	0.26

BP: Blood pressure, LV: Left ventricle, RV: Right ventricle, PAP: Pulmonary artery pressure, MPI: Myocardial performance index

and ABG values between those patients. The demographic and clinical properties of patients who died compared to those who survived were presented in Table 5. Cardiovascular risk factors, clinical and echocardiographic findings were not different between patients who died and who survived. Those were presented in Table 6. And, there were no significant correlations among respiratory and cardiac findings.

DISCUSSION

In this study, we detected that frequency of hypertension and paroxysmal atrial fibrillation were higher and heart rates were higher in kyphoscoliosis patients with chronic respiratory failure. Despite the normal dimensions and systolic functions, LV diastolic functions worsened and filling pressures increased in kyphoscoliosis patients. Otherwise, despite the normal dimensions, RV systolic and diastolic functions worsened and filling pressures increased. Furthermore, mean pulmonary artery pressure was found to be increased and inversely correlated with PaO_2 in kyphoscoliosis patients. Cor pulmonale was correlated with worsened PaO_2 values. Mortality was not correlated with cardiovascular findings.

Increased sympathetic activity in chronic respiratory failure was demonstrated by decreased heart rate variability[10]. In addition to this, parasympathetic dysfunction was detected to be common in COPD patients with respiratory distress in a previous study[11]. In patients with chronic respiratory failure, sympathovagal balance is in favour for sympathetic tone. Increased heart rate and AF are independent indicators for mortality[10-13]. Increased mortality might be associated with malignant arrhythmia related to increased sympathetic activation. In this study, the heart rate of kyphoscoliosis patients was higher than that of those in the control group, and frequency of atrial fibrillation was increased with respect to expected atrial fibrillation frequency of 0.4-1.4% in that age group in the population[12,13].

Coronary artery disease is another important reason for cardiovascular mortality. Frequency of hypertension, an important risk factor for coronary artery disease, was higher in severe chronic respiratory failure patients and it was declared to be due to chronic hypoxemia[14]. Frequency of hypertension in kyphoscoliosis patients was higher than expected frequency (~20%) in the same age group of the communityand the control group in this study[15]. The frequency of smoking, a major risk factor for coronary artery disease, was higher in kyphoscoliosis patients; however hyperlipidemia, another major risk factor for coronary artery disease, was not detected in any patient. Despite increased risk factors, overt coronary artery disease was not present in any of the patients.

Table 3. Comparisons of patients with and without cor pulmonale for demographic, clinical and laboratory specifications

	Patients with cor pulmonale (n: 4)	Patients without cor pulmonale (n: 19)
Age (years)	58.1 ± 17.2	53.4 ± 13.3
Male gender	2 (50.0%)	13 (68.0%)
NYHA Functional class: I/II/III/IV	0/2 (50.0%)/2 (50.0%)/0	0/16 (84.2%)/2 (10.5%)/1 (5.3%)
NIV Device: BPAP/BPAP ST/BPAP S	1 (25.0%)/ 3 (75.0%)/0	7 (36.8%)/10 (52.6%)/2 (10.5%)
NIV duration (months)*	24.2 (22.0 to 30.0)	37.3 (30.0 to 54.0)
Daily NIV use (hours)*	5.0 (3.4 to 8.3)	8.0 (6.4 to 10.2)
Device compliance	3 (75.0%)	18 (94.7%)
EPAP (cm H_2O)	6.0 ± 0.2	5.3 ± 0.9
IPAP (cm H_2O)	20.1 ± 0.4	16.5 ± 6.6
LTOT	3 (75.0%)	16 (84.2%)
Total hospitalization rates: 0/1/2/≥3 times	0/1(25.0%)/0/3 (75.0%)	0/6 (31.6%)/1 (5.3%)/12 (63.2%)
RICU hospitalization rates in last year: 0/1/2/≥3 times	0/4(100.0%)/0/0	6 (31.6%)/7 (36.8%)/3 (15.8%)/3 (15.8%)
Previous intubation rates: 0/1/2/≥3 times	4 (100.0%)/0/0/0	13 (68.4%)/4 (21.1%)/1 (5.3%)/1 (5.3%)
Previous thoracic operation	0	2 (10.5%)
Tracheostomized	0	2 (10.5%)
pH	7.40 ± 0.03	7.38 ± 0.05
$PaCO_2$ (mmHg)	53.3 ± 10.6	57.8 ± 11.55
PaO_2 (mmHg)	56.4 ± 5.1	66.7 ± 10.7
HCO_3 (mmol)	30.3 ± 6.2	32.5 ± 6.3
BE (mmol)	6.10 ± 2.77	7.56 ± 3.76
SaO_2 (%)	87.1 ± 5.7	88.1 ± 8.6
FVC volume (mL)*	800.0 (703.0-1010.0)	850.0 (798.0-1085.0)
FVC % predicted*	30.0 (26.0-36.0)	32.0 (25.0-44.0)
FEV1 volume (mL)*	685.0 (618.0-955.0)	760.0 (677.0-895.0)
FEV1 % predicted*	35.1 (27.2-37.1)	34.3 (26.2-42.3)
FEV1/FVC (%)*	89.1 (77.3-96.4)	84.2 (77.4-90.1)

NYHA: New York Heart Association, NIV: Noninvasive ventilation, BiPAP: Bi-level positive airway pressure, BiPAP/ST: Breath-time assured BiPAP, BiPAP/S: Pressure support for spontaneous breath BiPAP, EPAP: Expiratory positive airway pressure, IPAP: Inspiratory positive airway pressure, LTOT: Long term oxygen therapy, RICU: Respiratory intensive care unit, $PaCO_2$: Partial arterial carbon dioxide pressure, SaO_2: Arterial oxygen saturation, PaO_2: Partial arterial oxygen pressure, FVC:Volume of forced vital capacity, FVC%: Percent of expected FVC, FEV1: Volume of forced vital capacity in one second, FEV1%: Percent of expected FEV1.
* Median (25-75 percentiles)

LV systolic and diastolic functions are also indicators of cardiovascular mortality[16]. It has been shown that systolic function of LV is related to mortality in chronic respiratory failure[17,18]. In our patient group, systolic functions and dimension of LV were normal. Diastolic functions were deteriorated in kyphoscoliosis patients when compared to the control group. Estimated LV filling pressures were higher. However, MPI, which evaluates both systolic and diastolic functions, was not significantly different from the control group. Deteriorated LV diastolic dysfunction is probably related to increased hypertension frequency.

The most important cardiovascular complication of chronic respiratory failure is pulmonary hypertension. When we evaluated all patient groups together, there was a moderate increase in mean pulmonary artery pressure value. The size of RV was normal, however systolic and diastolic functions were found to be deteriorated. This condition is thought to be due to increase in pulmonary artery pressure value as it occurs in other chronic respiratory failure patients. However, in many circumstances, it could be evaluated as the early phase of heart failure because of initial diastolic function deterioration followed by systolic dysfunction[19]. If right heart failure develops in the setting of pulmonary disease, it is named as cor pulmonale. Generally, cor pulmonale develops in severe chronic respiratory failure cases. However, cor pulmonale was not detected in all patients with chronic respiratory failure. The frequency of cor pulmonale is variable according to the

Table 4. Comparisons of patients with and without cor pulmonale for cardiovascular risk factors and findings

	Patients with cor pulmonale (n: 4)	Patients without cor pulmonale (n: 19)
Smoking; ex smoker	2 (50.0%); 2 (100.0%)	11 (57.9%); 10 (90.9%)
Hypertension (%)	3 (75.0%)	8 (42.1%)
Diabetes mellitus (%)	0	2(10.5%)
Office heart rate (per minute)	89.6 ± 15.6	92.8 ± 13.6
Office systolic BP (mmHg)	128.3 ± 23.5	132.2 ± 20.1
Office diastolic BP (mmHg)	76.3 ± 11.7	84.0 ± 13.6
24 hours heart rate (per minute)	83.3 ± 13.1	86.2 ± 14.5
Paroxysmal atrial fibrillation (%)	0	5 (26.3%)
LV EF	64.1 ± 2.2	64.5 ± 3.1
RV end-diastolic area (cm^2)	34.5 ± 3.9	22.6 ± 3.1
RV fractional area change %	26.9 ± 4.6	42.1 ± 7.3
Mean PAP (mmHg)	37.8 ± 10.1	24.9 ± 8.5
Mitral lateral e'/a'	0.94 ± 0.38	0.74 ± 0.25
LV E/e'	8.14 ± 3.20	9.88 ± 4.49
Tricuspid lateral e'/a'	0.88 ± 0.33	0.69 ± 0.30
RV E/e'	5.1 ± 2.2	8.4 ± 4.7
LV MPI index	0.57 ± 0.22	0.60 ± 0.18
RV MPI index	0.76 ± 0.22	0.55 ± 0.17

BP: Blood pressure, LV: Left ventricle, RV: Right ventricle, PAP: Pulmonary artery pressure, MPI: Myocardial performance index.

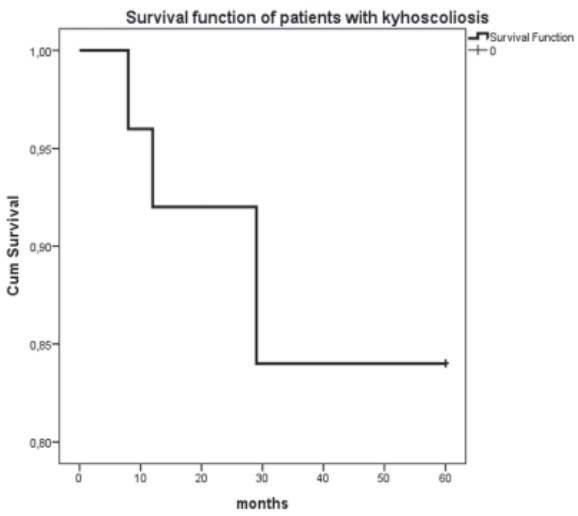

Figure 1. Kaplan Meier Survival curve was shown in five year follow-up.

Table 5. Comparisons of died and survived patients for demographic, clinical and laboratory specifications

	Died patients (n: 4)	Survived patients (n: 19)
Age (years)	56.4 ± 8.9	53.4 ± 13.9
Male gender	4 (100.0%)	15 (79.0%)
NYHA Functional class: I/II/III/IV	0/2 (50.0%)/ 2(50.0%)/0	0/16 (84.2%)/ 2 (10.5%)/ 1 (5.3%)
NIV Device: BPAP/ BPAP ST / BPAP S	1 (25.0%)/ 2 (50.0%)/ 1 (25.0%)	6 (31.6%)/ 12 (63.2%)/ 1 (5.3%)
NIV duration (months)*	47.0 (29.0 to 41.0)	35.0 (24.0 to 54.0)
Daily NIV use (hours)*	7.0 (4.5 to 6.0)	8.2 (5.9 to 10.1)
Device compliance	4 (100.0%)	17 (89.5%)
EPAP (cm H_2O)	5.0 ± 0.2	5.4 ± 0.9
IPAP (cm H_2O)	12.1 ± 2.8	17.7 ± 6.4
LTOT	4 (100.0%)	15 (79.0%)
Total hospitalization rates: 0/1/2/≥3 times	0/1 (25.0%)/ 1 (25.0%)/ 2 (50.0%)	0/6 (31.6%) / 0/13 (68.4%)
RICU hospitalization rates in last year: 0/1/2/≥3 times	1 (25.0%)/ 2 (50.0%)/ 1 (25.0%)/ 0	5 (26.3%) / 9 (47.4%) / 2 (10.5%) / 3 (15.8%)
Previous intubation rates: 0/1/2/≥3 times	2 (50.0%)/ 2 (50.0%)/ 0/ 0	15 (79.0%)/ 2 (10.5%)/ 1 (5.3%)/ 1 (5.3%)
Previous thoracic operation	0	2 (10.5%)
Tracheostomized	0	2 (10.5%)
pH	7.38 ± 0.03	7.38 ± 0.06
$PaCO_2$ (mmHg)	49.1 ± 9.66	56.9 ± 10.65
PaO_2 (mmHg)	66.7 ± 3.9	64.2 ± 11.7
HCO_3 (mmol)	29.6 ± 5.8	32.2 ± 5.3
BE (mmol)	5.12 ± 1.67	7.96 ± 3.66
SaO_2(%)	92.1 ± 3.4	87.2 ± 8.5
FVC volume (mL)*	890.0 (830.0-1880.0)	830.0 (725.0-1055.0)
FVC % predicted*	30.0 (24.0-6.0)	30.0 (26.0-40.0)
FEV1 volume (mL)*	850.0 (730.0-1400.0)	730.0 (625.0-890.0)
FEV1 % predicted*	34.0 (28.0-70.0)	34.0 (25.0-39.0)
FEV1/FVC (%)*	84.0 (74.0-95.0)	84.0 (77.0-92.0)

NYHA: New York Heart Association, NIV: Noninvasive ventilation, BiPAP: Bi-level positive airway pressure, BiPAP/ST: Breath-time assured BiPAP, BiPAP/S: Pressure support for spontaneous breath BiPAP, EPAP: Expiratory positive airway pressure, IPAP: Inspiratory positive airway pressure, LTOT: Long term oxygen therapy; RICU: Respiratory intensive care unit, $PaCO_2$: Partial arterial carbon dioxide pressure; SaO_2: Arterial oxygen saturation, PaO_2: Partial arterial oxygen pressure, FVC: Volume of forced vital capacity, FVC%: Percent of expected FVC, FEV1: Volume of forced vital capacity in one second, FEV1%: Percent of expected FEV1.
*median (25-75 percentiles)

Table 6. Comparisons of died and survived patients for cardiovascular risk factors and findings

	Died patients (n: 4)	Survived patients (n: 19)
Smoking; ex smoker	3 (75.0%); 2 (66.7%)	10 (52.6%); 10 (100.0%)
Hypertension (%)	1 (25.0%)	10 (52.6%)
Diabetes mellitus (%)	0	2 (10.5%)
Office heart rate (per minute)	83.5 ± 14.5	94.7 ± 12.7
Office systolic BP (mmHg)	127.2 ± 6.8	132.7 ± 22.1
Office diastolic BP (mmHg)	79.8 ± 14.2	83.7 ± 13.5
24 hours heart rate (per minute)	77.2 ± 11.2	88.2 ± 13.8
Paroxysmal atrial fibrillation (%)	1 (25.0%)	4 (21.1%)
LV EF	64.3 ± 2.3	64.4 ± 2.9
RV end-diastolic area (cm^2)	24.5 ± 2.9	24.8 ± 3.8
RV fractional area change %	39.5 ± 4.3	39.2 ± 8.2
Mean PAP (mmHg)	24.5 ± 13.1	27.9 ± 10.7
Mitral lateral e'/a'	0.74 ± 0.16	0.78 ± 0.3
LV E/e'	9.12 ± 0.73	9.65 ± 4.75
Tricuspid lateral e'/a'	0.82 ± 0.29	0.70 ± 0.32
RV E/e'	6.7 ± 1.2	7.4 ± 4.9
LV MPI index	0.72 ± 0.15	0.63 ± 0.20
RV MPI index	0.63 ± 0.25	0.58 ± 0.16

BP: Blood pressure, LV: Left ventricle, RV: Right ventricle, PAP: Pulmonary artery pressure, MPI: Myocardial performance index

study group and the cor pulmonale definition[19,20]. As such, the frequency of cor pulmonale in severe COPD has been declared in a wide range as 7.5-80%[20,21]. As it can be expected with its frequency in the community, COPD is the etiologic factor in 80% of cor pulmonale cases[20]. Restrictive lung disease is a rare cause and kyphoscoliosis causing restriction due to thorax deformity has only been declared as case reports[22,23]. In our study, cor pulmonale was detected with similar frequency as other patient groups with chronic respiratory failure. It has been detected that cor pulmonale had no relation with pulmonary functions in previous studies[20]. In our study it was found that in cor pulmonale patients, PaO_2 values were lower than that in patients without cor pulmonale, but spirometry results were similar. However, there was no significant difference according to age, duration of NIV use and daily device use.

Nocturnal hypoventilation, acute respiratory distress and increase in pulmonary artery pressure are seen in kyphoscoliosis and it has been declared that frequency of cor pulmonale has increased in relation to this[24,25]. The increased breathing work and reduced respiratory muscle activity during rapid eye movement (REM) sleep causes hypercapnia, which is seen at this time before it develops during the deeper stages of non-rapid eye movement (NREM) sleep and later, wakefulness[26,27]. It has been shown that nocturnal NIV in kyphoscoliosis patients has improved respiratory distress and has had benefits for symptoms, as it has in many other severe respiratory distress patients[28,31]. Small improvements in vital capacity, functional residual capacity, maximum inspiratory and expiratory mouth pressures, inspiratory muscle endurance and respiratory drive have also been shown[32]. Improvement has been shown in daytime PaO_2 and $PaCO_2$, and night time $PaCO_2$ levels, as well as the quality of life. Moreover, there was a significant increase in exercise capacity in respiratory failure patients using NIV[33,34]. Pulmonary hemodynamic has also been shown to be improved significantly after one year of NIV in patients with chest wall deformity[35]. It was declared that NIV improved cardiovascular parameters (sympathovagal stability) in patients with respiratory distress either due to COPD or other reasons[36,37]. There is no data for kyphoscoliosis. This condition is the most probable one for improvement due to facilitation of inspiratory and expiratory movements of the thorax. Although there is no exact data for how NIV improved cardiovascular status, it could be related to the limitation of sympathetic stimulation with the improvement of respiratory distress[37]. Besides, it was shown that decreased respiratory rate in COPD patients reduced sympathetic stimulation[38]. and it was declared that application of positive airway pressure with NIV might influence baroreceptor reflexes[39]. As a result, NIV yields normalization of sympathovagal stability. There is no sudden cardiac death was seen in this study for five years follow up in despite of the advanced disease. This result might be due to the positive effects of NIV on sympathovagal stability. Additionally, sudden cardiac death and malignant arrhythmias is very rare in patients with pulmonary arterial hypertension with right ventricular dysfunction unlike the in patients with left ventricular dysfunction[40]. Kyphoscoliosis similarly effects right ventricle and same immune mechanism might be has function against the malignant arrhythmia.

LIMITATIONS

The most important limitation of this study is the control group properties, as the samples were chosen from volunteers without respiratory distress. As the aim of the study was to evaluate risk despite treatment, the volunteers without respiratory distress were matched. Furthermore, deprivation of the patients from a proven intervention might be unethical. The positive effect of NIV on the physical findings of patients might have hidden the status of co-morbidities. However, this effect might be limited as all analysis was done during the day when patients did not use NIV. One drawback of our study was that biochemical parameters, such as natriuretic peptide, which demonstrates cardiac strain, were not studied.

CONCLUSION

Hypertension and paroxysmal atrial fibrillation are more frequent. The left ventricle is slightly affected while the right ventricle is severely affected, and pulmonary artery pressure is increased in kyphoscoliosis patients under long term NIV

treatment. Especially in patients with cor pulmonale, the dimensions of RV were larger and systolic functions were deteriorated. Cor pulmonale developed with similar frequency in kyphoscoliosis as in the case of other pulmonary diseases. The cases with cor pulmonale had lower PaO_2. However, there is no correlation between cardiovascular findings and mortality on five years follow up. But, limited patient counts could be concealed the correlations. So this study impresses that, besides administering NIV treatment, those patients should be followed closely and treated in terms of cardiovascular event.

ABBREVIATION LIST

NIV: non-invasive ventilation
RICU: respiratory intensive care unit
BiPAP: bi-level positive airway pressure
BİPAP/ST: bi-level positive airway pressure/breath-time assured
BiPAP/S: Bi-level positive airway pressure/pressure support for spontaneous breath
EPAP: Expiratory positive airway pressure
IPAP: Inspiratory positive airway pressure
ABG: Arterial blood gas
LV: Left ventricle
RV: Right ventricle
MPI: Myocardial performance index
FVC: Volume of forced vital capacity
FVC%: Percentage of expected FVC
FEV1: Volume of forced vital capacity in one second
$PaCO_2$: Partial carbon dioxide pressure
PaO_2: Partial oxygen pressure
SaO_2: Arterial oxygen saturation

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article. Study has no financial support.

AUTORSHIP CONTRIBUTIONS

Concept/Design: YK, HK, ZK, GA, ÖY, NA, MY, GG, AE
Analysis/Interpretation: ZK, GA, MY, GG
Data acquisition: YK, HK, GA, NA, GG
Writing: YK, HK, ÖY
Critical revision: AE, ZK, NA, MY, GA, GG
Final approval: All of authors

REFERENCES

1. Consensus Conference. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation - a consensus conference report. Chest 1999;116:521-34.
2. Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? Eur Respir J 2003;22:525-8.
3. Karakurt Z, Güven AO, Moçin OY, Karavelioğlu Y, Güngör G, Altınöz H, et al. Six minute walking distance in kyphoscoliosis patients with chronic respiratory failure. Multidiscip Respir Med 2010;5:244-9.
4. Dabestani A, Mahan G, Gardin JM, Takenaka K, Burn C, Allfie A, et al. Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography. Am J Cardiol 1987;59:662-8.
5. Budev MM, Arroliga AC, Wiedemann HP, Matthay RA. Cor pulmonale: an overview. Semin Respir Crit Care Med 2003;24:233-44.
6. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010; 23:685-713; quiz 786-8.
7. Gottdiener JS, Bednarz J, Devereux R, Gardin J, Klein A, Manning WJ, et al. American Society of Echocardiography recommendations for use of echocardiography in clinical trials. J Am Soc Echocardiogr 2004;17:1086-119.
8. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;152:1107-36.
9. Clair WK, Wilkinson WE, McCarthy EA, Page RL, Pritchett EL. Spontaneous occurrence of symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia in untreated patients. Circulation 1993;87:1114-22.
10. Heindl S, Lehnert M, Criée CP, Hasenfuss G, Andreas S. Marked sympathetic activation in patients with chronic respiratory failure. Am J Respir Crit Care Med 2001;164:597-601.
11. Tug T, Terzi SM, Yoldas TK. Relationship between the frequency of autonomic dysfunction and the severity of chronic obstructive pulmonary disease. Acta Neurol Scand 2005;112:183-8.
12. Stewart S, Hart CL, Hole DJ, McMurray JJ. Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study. Heart 2001;86:516-21.
13. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J 2006;27:949-53.
14. de Lucas-Ramos P, Izquierdo-Alonso JL, Rodríguez-González Moro JM, Bellón-Cano JM, Ancochea-Bermúdez J, Calle-Rubio M, et al. [Cardiovascular risk factors in chronic obstructive pulmonary disease: Results of the ARCE study]. Arch Bronconeumol 2008;44:233-8.
15. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al. Reappraisal of European guidelines on hypertension management: A European Society of Hypertension Task Force document. Blood Press 2009;18:308-47.
16. Tonelli AR, Plana JC, Heresi GA, Dweik RA. Prevalence and prognostic value of left ventricular diastolic dysfunction in idiopathic and heritable pulmonary arterial hypertension. Chest 2012;141:1457-65.
17. Gale CP, White JE, Hunter A, Owen J, Allen J, Watson J, et al. Predicting mortality and hospital admission in patients with COPD: significance of NT pro-BNP, Clinical and echocardiographic assessment. J Cardiovasc Med 2011;12:613-8.
18. Dursun D, Dursunoğlu N, Kuru Ö, Özkurt S, Gür Ş, Kiter G, et al. The effect of continuous positive airway pressure on blood pressure and left ventricular structure in male patients with obstructive sleep apnea. Turk Kardiyol Dern Ars 2006;34:496-503.
19. Han MK, McLaughlin VV, Criner GJ, Martinez FJ. Pulmonary diseases and the heart. Circulation 2007;116:2992-3005.
20. Weitzenblum E, Chaouat A. Cor pulmonale. Chron Respir Dis 2009;6:177-85.
21. Vizza CD, Lynch JP, Ochoa LL, Richardson G, Trulock EP. Right and left ventricular dysfunction in patients with severe pulmonary disease. Chest 1998;113:576-83.
22. Noble JS, Davidson JA. Cor pulmonale presenting in a patient with congenital kyphoscoliosis following intercontinental air travel. Anaesthesia 1999;54:361-3.
23. Ye YQ. [Kyphoscoliosis and cor pulmonale (report of 5 cases and review of the literature]. Zhonghua Jie He He Hu Xi Xi Ji Bing Za Zhi 1986;9:335-7,381-2.

24. Coccagna, G, Lugaresi, E. Arterial blood gases and pulmonary and systemic arterial pressure during sleep in chronic obstructive pulmonary disease. Sleep 1978;1:117-24.
25. Sawicka EH, Branthwaite MA. Respiration during sleep in kyphoscoliosis. Thorax 1987;42:801-8.
26. Midgren B, Petersson K, Hansson L, Eriksson L, Airikkala P, Elmqvist D. Nocturnal hypoxaemia in severe scoliosis. Br J Dis Chest 1988;82:226-36.
27. Hoeppner VH, Cockcroft DW, Dosman JA, Cotton DJ. Invasive nighttime ventilation improves respiratory failure in secondary kyphoscoliosis. Am Rev Respir Dis 1984;129:240-3.
28. Gonzalez C, Ferris G, Diaz J, Fontana I, Nuñez J, Marín J. Kyphoscoliotic ventilatory insufficiency: effects of long-term intermittent positive-pressure ventilation. Chest 2003;124:857-62.
29. Adıgüzel N, Karakurt Z, Güngör G, Moçin O, Balcı M, Saltürk C, et al. Management of kyphoscoliosis patients with respiratory failure in the intensive care unit and during long term follow up. Multidiscip Respir Med 2012;7:30.
30. Esquinas AM, Matsuoka Y, Adıgüzel N, Karakurt Z. Intensive care and non-invasive mechanical ventilation in kyphoscoliosis: Are new perspectives still needed? Multidiscip Respir Med 2013;8:31.
31. Hill NS, Eveloff SE, Carlisle CC, Goff SG. Efficacy of nocturnal nasal ventilation in patients with restrictive thoracic disease. Am Rev Respir Dis 1992;145:365-71.
32. Schönhofer B, Köhler D. Effect of non-invasive mechanical ventilation on sleep and nocturnal ventilation in patients with chronic respiratory failure. Thorax 2000;55:308-13.
33. Jackson M, Kinnear W, King M, Hockley S, Shneerson J. The effects of five years of nocturnal cuirass-assisted ventilation in chest wall disease. Eur Respir J 1993;6:630-5.
34. Zaccaria S, Zaccaria E, Zanaboni S, Patessio A, Braghiroli A, Spada EL, et al. Home mechanical ventilation in kyphoscoliosis. Monaldi Arch Chest Dis 1993;48:161-4.
35. Schönhofer B, Barchfeld T, Wenzel M, Köhler D. Long term effects of non-invasive mechanical ventilation on pulmonary haemodynamics in patients with chronic respiratory failure. Thorax 2001;56:524-8.
36. Sin DD, Wong E, Mayers I, Lien DC, Feeny D, Cheung H, et al. Effects of nocturnal noninvasive mechanical ventilation on heart rate variability of patients With Advanced COPD. Chest 2007;131:156-63.
37. Naughton MT, Benard DC, Liu PP, Rutherford R, Rankin F, Bradley TD. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 1995;152:473-9.
38. Raupach T, Bahr F, Herrmann P, Luethje L, Heusser K, Hasenfuss G, et al. Slow breathing reduces sympathoexcitation in COPD. Eur Respir J 2008;32:387-92.
39. Tkacova R, Dajani HR, Rankin F, Fitzgerald FS, Floras JS, Douglas Bradley T. Continuous positive airway pressure improves nocturnal baroreflex sensitivity of patients with heart failure and obstructive sleep apnea. J Hyperters 2000;18:1257-62.
40. Hoeper MM, Galie N, Murali S, Olschewski H, Rubenfire M, Robbins IM, et al. Outcome after cardiopulmonary resuscitation in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2002;165:341-4.