Noninvasive Ventilation in Chronic Respiratory Failure: Effects on Quality of Life

Vassiliki Tsolaki Chaido Pastaka Konstantinos Kostikas
Eleni Karetsi Andreas Dimoulis Andriani Zikiri Aggela Koutsokera
Konstantinos I. Gourgoulidis

Respiratory Medicine Department, University of Thessaly Medical School, Larissa, Greece

Key Words

Chronic hypercapnic respiratory failure • Chronic obstructive pulmonary disease • Health-related quality of life • Neuromuscular disease • Noninvasive ventilation • Obesity hypoventilation syndrome • Restrictive thoracic disorders

Abstract

Background: Noninvasive ventilation (NIV) has been found to be an essential technique to treat chronic respiratory failure (CRF) resulting from restrictive thoracic disorders (RTD). The last decades were characterized by the expansion of NIV to treat patients suffering from various other conditions, such as chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome (OHS). **Objectives:** The aim of this study was to evaluate the effect of NIV on health-related quality of life (HRQoL) of patients with CRF during 2 years and to identify parameters associated with changes in HRQoL. **Methods:** Ninety-one patients with CRF [35 COPD; 17 RTD; 28 OHS; 11 neuromuscular diseases (NMD)] participated. HRQoL was assessed with the SF-36 questionnaire.

Additional measurements included blood gases, pulmonary function tests, dyspnea, daytime sleepiness, exacerbations and hospitalizations. The patients were evaluated every 3–6 months. **Results:** Improvements in SF-36 physical component summary (PCS, $p < 0.0001$) and mental component summary (MCS, $p < 0.0001$) scores in RTD and MCS in OHS ($p = 0.01$) and COPD ($p = 0.003$) were observed by the third month. PCS in OHS and COPD patients improved by the sixth month ($p = 0.003$ and $p < 0.0001$, respectively). NMD patients did not present improvements in HRQoL. Improvements in HRQoL were associated with improvements in PaO_2 and dyspnea in COPD patients, and with total hours of daily ventilator use, improvement in dyspnea, pressure support and expiratory positive airway pressure in RTD patients. **Conclusion:** Home NIV is consistently effective in improving HRQoL and physiological parameters in patients with CRF. Randomized trials to identify subgroups of COPD responders are justified by our results.

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Introduction

Home noninvasive ventilation (NIV) represents an effective intervention for the management of chronic respiratory failure (CRF), primarily in patients suffering from chest wall and neuromuscular disorders (NMD) [1–3]. The last decades were characterized by the expansion of NIV for the treatment of patients suffering from other conditions, including chronic obstructive pulmonary disease (COPD) and obesity hypoventilation syndrome (OHS) [4, 5].

Patients with chronic alveolar hypoventilation due to neuromuscular and restrictive chest wall disorders have severely impaired health-related quality of life (HRQoL), especially in areas of functional health. Age, the underlying disease and the severity of hypoventilation relate to these decrements in HRQoL [6]. In patients with COPD and CRF, there is an increased impact of the disease on the patients' well-being, with the reduction in daily activities being one of the main consequences [7]. Studies have shown that NIV has a positive impact on HRQoL, regardless of the underlying cause of CRF [1, 5, 8–17]. However, the most recent randomized controlled trial of NIV in COPD patients has shown an improvement in survival, yet at the cost of worsening quality of life [18]. Moreover, HRQoL in patients receiving NIV has been shown to be influenced by the degree of dyspnea and the number of hospital admissions [19], whereas our group has shown that the only independent predictor of the change in HRQoL after 1 year of NIV in stable hypercapnic COPD patients was the change in dyspnea [16]. However, there are no studies in the literature that have been designed to evaluate the factors that govern changes in HRQoL in patients on NIV, a modality that has been found to be cost saving compared to long-term oxygen therapy in this group of patients [20].

The aim of the present longitudinal study was to evaluate the effect of NIV on the HRQoL of patients with CRF during 2 years of follow-up and to assess parameters associated with the changes in HRQoL. Physiological outcomes, morbidity and mortality during 2 years of follow-up were also evaluated.

Methods

Patients

The patients were classified into four groups: COPD; restrictive thoracic disorders (RTD); OHS, and NMD. COPD was diagnosed according to the ATS/ERS guidelines [21]. All study participants had CRF and inclusion criteria met the current guide-

lines for the initiation of NIV in different patient groups [22]. Patients with symptoms of nocturnal hypoventilation (fatigue, dyspnea, morning headaches) combined with daytime hypercapnia (partial dioxide pressure, PaCO_2 , ≥ 45 mm Hg for patients with RTD and NMD, and $\text{PaCO}_2 \geq 50$ mm Hg for COPD patients) met inclusion criteria. In the OHS group, we included patients with a BMI >30 , with hypercapnia ($\text{PaCO}_2 > 45$ mm Hg) and hypoxemia (partial oxygene pressure, PaO_2 , <70 mm Hg) in the absence of other diseases. These patients had an overnight trial of continuous positive airway pressure titration and those patients who presented sustained hypoventilation despite the elimination of apneas were switched to NIV. All patients were screened for sleep apnea with nocturnal polysomnography. All patients with an apnea-hypopnea index $>10/\text{h}$ were excluded from the study, apart from patients with OHS. The study protocol was approved by the ethics committee of our hospital and written informed consent was obtained from all study participants.

Patients with acute respiratory failure ($\text{pH} < 7.35$ and symptoms such as increasing cough, purulent sputum, need for antibiotics) or patients with an exacerbation during 4 weeks preceding recruitment were excluded. Patients with forms of respiratory support other than NIV with a bilevel positive airway pressure device and patients with poor compliance with the use of the ventilator (i.e. mean use <4 h/day) at the first follow-up visit were also excluded.

Ventilatory Support

Patients were hospitalized for 2–3 days during the initial application of NIV, in order to ensure maximal compliance. The modality of NIV was pressure support ventilation delivered by a variable positive airway pressure device (VPAP III ST, ResMed, Sydney, N.S.W., Australia), set in the spontaneous/timed mode with a backup respiratory rate of 8–14 breaths $\cdot \text{min}^{-1}$ as previously described [16]. Inspiratory and expiratory positive airway pressures (IPAP and EPAP, respectively) were adjusted according to the patient's comfort and synchrony with the ventilator and a marked reduction in the use of accessory muscles. For the first 2 h from the initiation of ventilation the patient was observed by a pulmonologist and a fully trained nurse, in order to assure a decrease in accessory respiratory muscle use and respiratory rate, check the patient's comfort of mask ventilation and possible air leaks of the system. Supplemental oxygen was added as needed in order to maintain oxygen saturation (SaO_2) between 88 and 92%. Arterial blood gases were measured 1 h after the initiation of ventilation. A 5% decrease in PaCO_2 values was considered as adequate ventilatory support. Subsequently, the patients and their relatives were trained in hospital until they were fully confident in using the ventilator. Technically skilled personnel installed the ventilator at the patients' home and provided full technical support when required. Humidification was used if necessary.

Physiological Measurements

Spirometry was performed with a dry spirometer (KoKo Legend, Ferraris, UK), according to the ATS guidelines [23]. Arterial blood gases were measured at rest with the patient breathing room air or with supplemental oxygen aiming to keep pulse oximetric saturation at 88–92%. Dyspnea was assessed with the Medical Research Council (MRC) dyspnea scale [24]. Subjective daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS) [25].

Health-Related Quality of Life

The evaluation of HRQoL was made using the validated Greek version of the SF-36 Health Survey (version 2) [26]. This instrument has successfully been used to evaluate HRQoL in patients with different causes of CRF receiving domiciliary noninvasive mechanical ventilation [1, 15, 27, 28], and our group has previous experience with COPD patients on NIV [16].

Study Protocol

Study participants were evaluated in the NIV outpatient clinic in the first, third, and sixth month, and every 6 months thereafter, until 2 years after the initial evaluation, except for patients with COPD who were evaluated at 3 monthly intervals. If a patient, of any study group, had an exacerbation (defined as a marked increase in dyspnea or lower respiratory tract infection requiring change in medication or hospital admission or pH <7.35) at any of those time points, measurements were obtained 1 month after the event. At every appointment, physical examination was performed and arterial blood gases, spirometry, MRC dyspnea, HRQoL and ESS were assessed. Additionally, the settings and the hours of ventilator use (as obtained from the machines' time counters) were evaluated, in order to determine proper compliance. During the follow-up period, patients underwent adjustments to NIV masks or ventilator settings as needed, in order to maintain patient-ventilator synchrony and optimize gas exchange and functional status. In particular, if the patient presented with worsened hypercapnia, we increased pressure support, while in hypoxemia, we increased the positive end-expiratory pressure levels. Additional measurements recorded included the number of exacerbations, hospital admissions, the number of in-hospital days, the need for intubation and treatment in intensive care units and the number of deaths during the follow-up period of 2 years.

Statistical Analysis

Data are presented as mean $\pm$ standard deviation (SD), with ranges in parentheses, unless otherwise mentioned. Comparisons between two groups were performed with independent-samples *t* tests, whereas comparisons among 3 or more groups were performed with one-way analyses of variance with appropriate post hoc tests (Bonferroni). In order to define determinants of the improvement in HRQoL at the end of the trial, stepwise multiple linear regression models were created. Kaplan-Meier curves were created for the evaluation of survival. The analysis of the NMD group was performed until the twelfth month as by the end of the trial only 1 patient in this group was still alive.

In order to define determinants of HRQoL, stepwise multiple linear regression models were created. Univariate analyses were performed using the change in physical component summary (PCS) and mental component summary (MCS) as the depended variable and the changes in arterial blood gases from baseline (Δ PaO₂, Δ PaCO₂), the changes in dyspnea and daytime sleepiness (Δ MRC, Δ ESS), along with the changes in pulmonary function tests (Δ FEV₁, Δ FVC), IPAP, EPAP, pressure support (IPAP – EPAP) and total hours of ventilator use were added as covariates. Statistically significant parameters in univariate analyses were added in multivariate regression analyses. *p* values <0.05 were considered statistically significant. Data were analyzed with SPSS 12.0 and Sigma Plot 8 software.

Results

Patients

A total number of 101 patients were entered in the study receiving NIV. Four patients refused regular visits at the hospital, 4 patients did not present in their first re-evaluation schedule and 2 patients did not use the ventilator for more than 4 h daily, thus leaving 91 patients eligible for follow-up. Thirty-five patients had COPD, 17 had RTD (8 post-tuberculous sequelae, 5 kyphoscoliosis and 4 thoracic cage abnormalities), 28 patients suffered from OHS, and 11 had NMD (10 patients with motor neuron disease and 1 with mitochondrial myopathy). The baseline characteristics of each group are shown in table 1. In total 72.5% of the patients required supplemental oxygen administration, all of them having COPD, thoracic cage disorders or OHS. The daily hours of ventilator usage were 9.2 ± 2.2 for the COPD group, 12 ± 2.6 for the patients with NMD, 9.6 ± 2.1 for those with RTD, 7.7 ± 2.5 for patients with OHS.

Physiological Outcomes

Spirometric parameters did not change significantly throughout the study period. The time courses of PaO₂ and PaCO₂ in the four groups are shown in figure 1a and b, respectively.

Dyspnea improved by the third month in RTD (3.5 ± 0.1 to 2.8 ± 0.6 , *p* = 0.001), by the first month in the OHS patients (4.0 ± 0.6 to 3.4 ± 0.9 , *p* = 0.003) and by the third month in the COPD group (4.0 ± 0.5 to 3.4 ± 0.6 , *p* = 0.001), which was maintained thereafter. The degree of dyspnea in patients with NMD remained unchanged until the twelfth month, when it showed significant deterioration (3.7 ± 0.8 to 4.3 ± 0.5 mm Hg, *p* = 0.002). ESS improved immediately in all patient groups (RTD: 7.6 ± 5.3 to 3.6 ± 2.6 , *p* = 0.001, COPD: 9.5 ± 5.1 to 5.0 ± 2.5 , *p* < 0.0001, OHS: 16.0 ± 3.1 to 7.6 ± 3.6 , *p* < 0.0001), with the exception of the NMD group (2.7 ± 3.8 to 0.8 ± 1.7 , *p* = 0.620).

Morbidity and Mortality

At the end of the second year of the trial, 71 exacerbations ($1.04 \text{ n}\cdot\text{patient}^{-1}\cdot\text{year}^{-1}$) had been recorded in the COPD group (45 in the 1st year and 26 in the second, 1.28 ± 2.00 vs. $0.74 \pm 1.40 \text{ n}\cdot\text{patient}^{-1}\cdot\text{year}^{-1}$, *p* = 0.194) and 357 days of hospitalization ($5.35 \text{ n}\cdot\text{patient}^{-1}\cdot\text{year}^{-1}$) (210 in the 1st year and 147 in the second, 6.00 ± 13.86 vs. $4.31 \pm 10.91 \text{ n}\cdot\text{patient}^{-1}\cdot\text{year}^{-1}$, *p* = 0.574). In the NMD group, 3 exacerbations were recorded ($0.09 \text{ n}\cdot\text{patient}^{-1}\cdot\text{year}^{-1}$), all of them in the 1st year, and 53 days of hospitalization

Table 1. Demographics of the study participants at baseline

	COPD (n = 35)	NMD (n = 11)	RTD (n = 17)	OHS (n = 28)
Age, years	67.1 ± 9.0	62.8 ± 11.0	65.8 ± 7.8	63.0 ± 9.9
Gender (M/F)	28/7	4/7	11/6	18/10
BMI	29.2 ± 4.8	23 ± 4.2	29.2 ± 0.9	41.7 ± 6.6
AHI, episodes/h	5.2 ± 6.8	3.2 ± 3.3	2.7 ± 2.4	28.8 ± 30.2
Smoking, pack-years	49.6 ± 33.1	0.0 ± 0.0	29.4 ± 22.8	32.3 ± 34.9
FEV ₁ , % predicted	35.2 ± 11.1	43.5 ± 7.9	45.9 ± 14.1	61.7 ± 18.7
FVC, % predicted	51.3 ± 17.1	42.2 ± 10.4	45.9 ± 17.3	62.5 ± 17.3
FEV ₁ /FVC, %	56.8 ± 10.5	76.6 ± 3.9	77.0 ± 7.4	79.1 ± 10.1
PaO ₂ , mm Hg	59.1 ± 6.5	67.5 ± 9.9	58.5 ± 3.3	60.1 ± 5.8
PaCO ₂ , mm Hg	53.9 ± 5.3	47.6 ± 5.2	52.1 ± 4.4	51.6 ± 6.2
pH	7.42 ± 0.03	7.41 ± 0.04	7.42 ± 0.03	7.43 ± 0.02
HCO ₃ ⁻ , mmol/l	35.4 ± 4.2	31.4 ± 1.6	33.9 ± 4.6	33.6 ± 3.6
IPAP, mm Hg	15.4 ± 1.9	14.4 ± 2.1	14.7 ± 2.4	16.3 ± 2.4
EPAP, mm Hg	5.4 ± 0.9	5.2 ± 0.4	5.0 ± 1.1	6.1 ± 1.0
LTOT, l/min	1.6 ± 0.9	n/a	1.4 ± 1.1	1.0 ± 1.9
Dyspnea, MRC scale	4.0 ± 0.5	3.7 ± 0.8	3.5 ± 0.6	4.0 ± 0.6
ESS score	9.5 ± 5.1	2.7 ± 3.8	7.6 ± 5.3	16.0 ± 4.0

Data are presented as mean ± SD. AHI = Apnea-hypopnea index; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; HCO₃⁻ = serum bicarbonate; LTOT = long-term oxygen therapy; n/a = not applicable.

Fig. 1. **a** Time course of arterial oxygen tension (PaO₂) during the study period in the four groups, i.e. COPD, RTD, OHS and NMD. Each time point represents the mean value. **b** Time course of arterial carbon dioxide tension (PaCO₂) during the study period in the four groups, i.e. COPD, RTD, OHS and NMD. Each time point

represents the mean value. **a, b** Significant differences from baseline at each time point are indicated as * $p < 0.05$ in the NMD group, as # $p < 0.05$, ### $p < 0.001$ in the COPD group, as +++ $p < 0.001$ in the RTD group, and as + $p < 0.05$, +++ $p < 0.001$ in the OHS group.

Table 2. SF-36 values at baseline

	COPD (n = 35)	NMD (n = 11)	RTD (n = 17)	OHS (n = 28)
SF-36 PF	13.42 ± 12.29	8.18 ± 18.20	19.70 ± 7.80	11.60 ± 10.47
SF-36 RP	25.17 ± 14.01	20.45 ± 11.21	37.13 ± 9.49*	25.22 ± 10.13
SF-36 RE	41.92 ± 15.90	32.87 ± 20.19	45.58 ± 9.32	33.03 ± 17.49
SF-36 EV	21.92 ± 14.68	25.56 ± 17.99	36.39 ± 11.31*	20.38 ± 12.10
SF-36 MH	34.07 ± 16.42	24.09 ± 14.28	48.23 ± 7.69*	30.71 ± 13.65
SF-36 SF	24.21 ± 19.54	10.22 ± 10.92	36.02 ± 13.89	24.10 ± 14.80
SF-36 P	60.62 ± 16.36	74.18 ± 10.37	78.58 ± 8.08*	59.21 ± 20.90
SF-36 GH	18.51 ± 13.96	14.54 ± 7.56	31.58 ± 7.00*	21.35 ± 13.72
SF-36 PCS	31.08 ± 4.41	32.48 ± 4.95	35.55 ± 2.66*	31.61 ± 3.88
SF-36 MCS	28.58 ± 8.12	23.63 ± 8.78	34.30 ± 5.15	26.32 ± 8.10

Data are presented as mean ± SD. PF = Physical function; RP = role physical; RE = role emotional; EV = vitality; MH = mental health; SF = social function; P = pain; GH = general health. Comparisons were made between the COPD group and the groups of NMD, RTD and OHS. Significant differences are indicated as * $p < 0.05$.

(2.42 n·patient⁻¹·year⁻¹), in the RTD group, 1 exacerbation (0.029 n·patient⁻¹·year⁻¹) was recorded during the 1st year and no hospitalization, whereas in the OHS group, there were 15 exacerbations (0.26 n·patient⁻¹·year⁻¹) (11 in the 1st year and 4 in the 2nd, 0.83 ± 0.70 vs. 0.44 ± 0.72 n·patient⁻¹·year⁻¹, $p = 0.014$) and 68 days of in-hospital stay (0.09 n·patient⁻¹·year⁻¹) (62 in the 1st year and 6 in the second, 3.77 ± 5.65 vs. 2.33 ± 5.14 , n·patient⁻¹·year⁻¹, $p = 0.292$).

Two patients required endotracheal intubation in the COPD group. The survival rate after 2 years of follow-up was 100% in the RTD group, 96.4% in the OHS group, 88.6% in the COPD group and 9.9% in the NMD group. The Kaplan-Meier curve showing the cumulative survival of all study groups is presented in figure 2.

Health-Related Quality of Life

The changes in HRQoL are presented in table 2. Apart from patients with NMD, all the other three study groups showed significant improvements in HRQoL. In patients with RTD, the PCS (35.5 ± 2.7 to 42.8 ± 4.8 , $p < 0.0001$) and MCS scores (34.3 ± 5.2 to 41.9 ± 2.7 , $p < 0.0001$) improved by the third month. In the OHS group, the PCS scores improved by the sixth month (31.6 ± 2.9 to 37.9 ± 7.6 , $p = 0.0031$), while the MCS scores improved earlier by the third month (26.3 ± 8.1 to 37.3 ± 10.2 , $p = 0.010$). The PCS scores in COPD patients improved by the sixth month (31.1 ± 4.4 to 38.4 ± 8.2 ; $p < 0.0001$) and the MCS scores by the third month (28.6 ± 8.1 to 39.0 ± 10.3 , $p = 0.003$). Concerning the patients in the NMD group, their

Fig. 2. Cumulative survival of the four groups on NIV after 2 years.

HRQoL did not change until the sixth month; in contrast, the PCS scores showed a significant deterioration from that time point and thereafter (32.5 ± 4.7 to 26.7 ± 2.5 , $p = 0.014$). Changes in PCS and MCS scores are presented in figure 3a, b.

Table 3. Determinants of the improvement in HRQoL in the different study groups

	Independent variable	Multiple R	B	Standard error	β	t	p value
Δ PCS							
COPD group	Δ PaO ₂	0.434	0.485	0.113	0.659	4.287	<0.0001
RTD group	hours	0.853	3.315	0.368	0.923	9.005	<0.0001
OHS group	–						
Δ MCS							
COPD group	Δ MRC	0.723	–4.515	1.926	–0.402	–2.344	0.029
RTD group	Δ MRC	0.998	28.755	4.079	1.651	7.049	<0.0001
	PS		9.753	0.377	1.349	25.866	<0.0001
	EPAP		–9.007	2.206	–0.956	–4.082	0.001
	Δ PaCO ₂		0.685	0.091	0.215	7.518	<0.0001
OHS group	–						

The analysis of the factors related to HRQoL and its change in the NMD group was made for month 12 as only 1 patient was still alive by the end of the study. For the same reason, this group was not included in the analysis for the total group of patients. Δ PCS = Change in physical component score; Δ MCS = change in mental component score; Δ PaO₂ = change in partial oxygen pressure; Δ PaCO₂ = change in partial dioxide pressure; Δ MRC = change in medical research council dyspnea level; PS = pressure support (IPAP – EPAP).

Determinants of HRQoL

The results of the stepwise multiple linear regression analysis for the determinants of HRQoL are presented in table 3. In patients with COPD, the improvement in PCS score was associated with the improvement in PaO₂ ($R^2 = 0.434$, $p < 0.0001$), while the improvement in dyspnea was the best determinant of the improvement in MCS score ($R^2 = 0.238$, $p = 0.029$). In patients with RTD, the improvements in PCS score were associated with the total hours of ventilator use per day ($R^2 = 0.853$, $p < 0.0001$), while predictors of improvement in MCS score were the improvement in dyspnea and PaCO₂, pressure support (IPAP – EPAP) and EPAP ($R^2 = 0.998$, $p < 0.0001$). No significant associations were identified for the changes in HRQoL in patients with OHS.

Discussion

In the present study, we have prospectively evaluated HRQoL in patients receiving home NIV over a period of 2 years. We have shown that patients with CRF of different origin (COPD, RTD and OHS) present improvements in physiological outcomes and HRQoL with the use of domiciliary NIV. PaO₂ and dyspnea in COPD patients, and the total hours of daily ventilator use, improvement in dyspnea and hypercapnia, pressure support and EPAP

in RTD patients were the major determinants of the improvement in HRQoL in patients receiving domiciliary NIV.

It has been shown that both general and disease-specific aspects of HRQoL increase following NIV. Improvements can be observed after 1 month of ventilator use and are maintained over a period of 1 year [17]. The present study extends this finding over a longer period of 2 years in various types of patients on home NIV. Although the changes in HRQoL were more profound in the RTD group, the overall changes in HRQoL in all three groups were comparable, with the COPD and OHS groups presenting similar changes. Moreover, in patients with NMD (mainly motor neuron disease) who presented rapid deterioration due to the nature of their underlying disease, home NIV improved arterial blood gases and maintained quality of life for several months.

For patients with RTD and NMD, NIV can improve symptoms related to chronic hypoventilation in the short term and prolong quality of life and survival in the long term [29]. This conclusion is based on a systematic review of the Cochrane Library and the data on HRQoL come from two studies including patients with NMD. In support of those data, we have shown that in NMD, and especially in patients with motor neuron disease, NIV may have an adjuvant role in preserving their HRQoL. Apparently, this group showed a transient maintenance in their

Fig. 3. a Time course of PCS during the study period in the four groups, i.e. COPD, RTD, OHS and NMD. Each time point represents the mean value with SD. **b** Time course of MCS during the study period in the four groups, i.e. COPD, RTD, OHS and NMD. Each time point represents the mean value with SD. **a, b** Signifi-

cant differences from baseline at each time point are indicated as * $p < 0.05$ in the NMD group, as # $p < 0.05$, ### $p < 0.001$ in the COPD group, as + $p < 0.05$, ††† $p < 0.001$ in the RTD group, and as † $p < 0.05$, ††† $p < 0.001$ in the OHS group.

quality of life regarding the improved sense of dyspnea when using NIV. In a similar manner, NIV has been proven efficient in improving HRQoL in patients with amyotrophic lateral sclerosis, another rapidly deteriorating NMD [11].

Patients with restrictive disorders have shown improvement in HRQoL after the establishment of NIV for 12 and 18 months [13, 15, 17]. We have extended this outcome over a period of 2 years. As for patients with OHS, it has been shown that HRQoL improves following continuous positive airway pressure therapy, and recently after 1 year of NIV application [12, 17]. Surprisingly, changes in HRQoL in OHS were comparable with COPD patients. NIV seems to be more efficient in COPD patients with higher BMI values, yet not having obstructive sleep apnea syndrome or OHS, patients traditionally known as the 'blue bloaters', and this is in line with other studies which included heavier patients [30], while studies including patients of the 'pink puffer' phenotype fail to show any clinical benefit [18, 31, 32].

The use of NIV in patients with chronic hypercapnic respiratory failure in the setting of severe stable COPD is not recommended yet, as existing data are inconsistent [33–35]. Interestingly, our data present positive effects of NIV on the HRQoL of COPD patients, in contrast to a recent randomized controlled trial that has shown improvement in survival at the cost of worsening quality of

life in those patients [18]. Both trials use the same questionnaire and statistically significant changes do not necessarily mean clinical change. However, our encouraging results could be explained by the motivation of patients, since we included in this study all the patients that agreed to be submitted to NIV and used ventilation adequately (i.e. >4 h/day) during follow-up. Additionally, we have provided close monitoring of all patients. This enabled us to re-evaluate patients' physical and psychological condition, check and reset parameters of the ventilator and encourage and advise our patients to use the ventilator properly and for more hours daily.

In the present study, we have evaluated predictive factors that influence changes in HRQoL in NIV users. Dyspnea was an independent predictor of the changes seen in quality of life in patients suffering from COPD and RTD and this is supported by previous findings [14, 16, 19, 36]. It seems that dyspnea ratings influence and predict general health status in a greater extent than do physiologic measurements in patients with symptomatic COPD [36], whereas dyspnea attacks have been found to negatively influence HRQoL even in the general population [37]. Dyspnea is associated with poorer quality of life in patients with alveolar hypoventilation due to kyphoscoliosis [38], and patients receiving NIV for CRF of different origin [19]. The present study shows that the application of NIV on a daily basis at home in patients with CRF re-

sults in improvement in the subjective conception of dyspnea, which is translated into a general improvement in the quality of life.

The improvement in arterial blood gases was an important factor for the improvement in HRQoL outcomes. The improvement in PaO₂ was the best predictor of the PCS in COPD patients, while the decrease in PaCO₂ was the best predictor of the MCS in the RTD group. Long-term oxygen therapy improves survival in patients with hypoxemic COPD, but has no effect on their quality of life [39]. Moreover, they present worse quality of life especially in the physical function domains [40]. Bilevel NIV has been found to have a positive impact on both arterial oxygen and carbon dioxide tension [34]. Patients without any improvements in arterial blood gases did not present improvements in HRQoL with NIV [18, 32]. Thus, we believe that the correction of arterial blood gas disturbances should be the goal of effective ventilation, being a possible underlying mechanism for HRQoL improvement.

The total hours of ventilator use was the most significant independent predictor of the improvement in physical functioning in patients with RTD. Data on the impact of the duration of ventilator use on physiologic outcomes have been inconsistent [41, 42]. Our data clearly support the need for compliance with NIV treatment in order to achieve the benefits of this treatment, especially in RTD. Pressure support (IPAP – EPAP) and EPAP were predictors of the change in MCS scores in patients with RTD and this is in line with previous findings [42]. Budweiser et al. [42] explored the impact of ventilation parameters on NIV users with RTD, showing that IPAP was the best predictor of improvement in lung volume and the amplitude of pressure (IPAP – EPAP) was the most important determinant of effective ventilation. It seems that pressure support, by correcting arterial blood gases, positively affects quality of life.

This study has certain limitations. Firstly, it is not a randomized controlled trial. However, the longitudinal design and the fact that we followed up the majority of our patients for 2 years adds value to our data. Another limitation is that in the NMD group we included mainly patients with motor neuron disease, a disease with a more rapid deterioration than other forms of NMD, e.g. Duchenne's muscular dystrophy [43]. As disease progressed, patients demonstrated deterioration in their health status. Due to impaired mobility they were often not able to reach the hospital, therefore the ventilator parameters could not be re-evaluated properly in those patients. All of those patients died at home, as neither they, nor their

families wanted to prolong their life, knowing the physical course of the disease. Ten of the 11 patients died before the completion of the 2-year follow-up. We believe that this limitation is partly compensated by the fact that in the analysis of HRQoL we included 1-year data for this group. A third limitation is that we used a generic questionnaire to evaluate HRQoL. It might have been preferable to use the Severe Respiratory Insufficiency Questionnaire, which has been specifically designed to measure HRQoL in patients receiving home mechanical ventilation. This instrument has been shown to have high psychometric properties and is capable of detecting changes in HRQoL. However, this questionnaire has not yet been validated in the Greek language, thus we chose to use the SF-36 questionnaire which is able to detect improvements in HRQoL in home NIV users, although not as comprehensively as the Severe Respiratory Insufficiency Questionnaire [17].

In conclusion, this study provides data on quality of life in NIV users in a large cohort of patients over a 2-year period. We have shown that home NIV is consistently effective in improving health-related outcomes, including quality of life, dyspnea and objective daytime sleepiness along with arterial blood gases, in patients with CRF resulting from various conditions. Moreover, patients with COPD presented a pattern of improvement in their HRQoL, resembling that seen in other groups (OHS, RTD), in which the use of NIV has proven to be efficient in improving HRQoL. The best predictors of the improvements in HRQoL were the improvements in PaO₂ and dyspnea in COPD patients, and the total hours of daily ventilator use, improvement in dyspnea, pressure support and EPAP in RTD patients. The results of our study further support the need for randomized trials for the identification of subgroups of COPD patients that will better respond to NIV.

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