Nocturnal non invasive ventilation in normocapnic cystic fibrosis patients: a pilot study

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Abstract. Background and aim: In patients with cystic fibrosis (CF) non-invasive ventilation (NIV) improves lung mechanics and gas exchange, and decreases the work of breathing. Domiciliary NIV is mainly used in hypercapnic patients with severe disease, because it counteracts the progression of lung functional impairment and it is often used as a useful “bridge” to lung transplantation. However, to date, there are no standardized criteria to indicate the effect of a precocious starting of NIV in patients with functional ventilation inhomogeneity without hypercapnia. In this pilot study we assessed whether an early NIV treatment might influence functional and clinical outcomes in CF patients. Methods: Six normocapnic CF patients were treated for one year with NIV. At baseline and after 1 year of NIV treatment, arterial gas analysis, spirometry, MBW to derive LCI, nocturnal cardio-respiratory polygraphy (PG), and Pittsburgh Sleep Quality Index (PSQI) were performed in all enrolled patients. Results: After one year, despite spirometric and LCI values remain statistically not modified, the number of infectious exacerbations was reduced by 50%. Conclusions: These results suggest that nocturnal NIV improves clinical conditions of stable CF patients. Finally, we suggest that this procedure can be useful to counteract the progression of lung disease even in normocapnic patients (www.actabiomedica.it)

Key words: cystic fibrosis, lung clearance index, nocturnal cardio-respiratory polygraphy, non-invasive ventilation, normocapnic; quality of life.

Introduction

In patients with cystic fibrosis (CF) non-invasive ventilation (NIV) improves lung mechanics and gas exchange, and decreases the work of breathing (1, 2). Domiciliary NIV is mainly used in hypercapnic patients with severe disease, because it counteracts the progression of lung functional impairment and it is often used as a useful “bridge” to lung transplantation (3). However, to date, there are no standardized criteria to indicate the effect of a precocious starting of NIV in patients with functional ventilation inhomogeneity without hypercapnia. On this regard, the Lung Clearance Index (LCI), derived from a multiple-breath washout of an inert gas (MBW), reflecting the distal airway status, has been recently proposed as a new tool to assess the ventilation inhomogeneity in the lungs of patients with CF (4). In fact, abnormal LCI values occur early in the life of these patients and reflect, more sensitively than spirometric values, the structural changes occurring in the lungs of patients with CF (4, 5).

The aim of this study was to assess whether a precocious starting of nocturnal NIV can be useful to improve clinical condition even in normocapnic awake CF patients and it can represent a procedure to coun-
teract the progression of lung diseases as well as quality of life score.

**Materials and Methods**

**Participants**

We studied a total of 6 nocturnal hypoxemic and daily normocapnic awake patients (2 males, 4 females, age 15-34 years) followed in our Cystic Fibrosis Centre, Respiratory Unit, Department of Clinical and Experimental Medicine, University of Catania.

Diagnosis of CF was based on a sweat chloride level above 60 mmol/L and a genetic test showing two pathogenic mutations in the CF transmembrane conductance regulator gene (6).

All patients were stable at initiation of the treatment. We defined as “stable” patients showing: 1) no disease exacerbation for at least one month before enrollment; 2) no decrease in FEV1 after at least one month since the last clinical evaluation.

Exclusion criteria included: diurnal hypoxemia and/or hypercapnia, significant nocturnal events of obstructive apneas and severe nocturnal hypoxemia (time of the night spent with a SaO2 below 90% >30% for adults and >10% for adolescents), history of pneumothorax/blebs and/or experiencing pulmonary exacerbations defined in accordance to the Fuchs criteria (7).

For all patients clinical records were available since they were followed in our Center from long time. We assessed demographic data, comorbidities, and the occurrence of pulmonary exacerbations.

Written informed consent was obtained from the patients or, in children and adolescents, from their parents. Ethical Committee from the Institutional Review Board approved the study.

**Study protocol**

At the baseline (day 1) arterial gas analysis, spirometry, MBW to derive LCI, and nocturnal cardio-respiratory polygraphy (PG) were performed in accordance to ERS guidelines (Exhalyzer D (EcoMedics AG, Duernent, Switzerland) (8), and American Academy of Sleep Medicine (AASM) standards (9). The Pittsburgh Sleep Quality Index (PSQI) was also recorded (10).

A NIV session for acclimatization pressure support ventilation (PSV)-ST was also performed by using a bi-level domiciliary ventilator (Astral 150) with nasal mask. The following parameters were adopted: inspiratory positive airway pressure (IPAP) 10 cmH2O and expiratory positive airway pressure (EPAP) 6 cmH2O.

Following the night of adaptation to NIV, set parameters for the use of home NIV were defined for each patient.

The adherence to the treatment was defined as at least 4 hours per night. Both the clinical status and the adherence to the treatment were assessed every 3 months.

At the end of the study (year 1), all enrolled patients underwent to spirometry, LCI, and nocturnal cardio-respiratory PG. The PSQI was also administered.

**Lung Function Tests**

**Spirometry**

Pulmonary function was measured in the laboratory using spirometry (Lungtest 1000, MES Ltd. 30-390 Krak.w, 56 Zawia street). FEV1% was measured as gold standard parameter for airflow obstruction assessment. The best spirometric measureof at least three attempts was recorded for analysis. Values were expressed as percent of predicted values, based on child age, gender, weight and height (11).

**Lung Clearance Index**

MBW was performing using 100% oxygen to washout resident nitrogen from the lung with the Exhalyzer D system (EcoMedics, Duernent, Switzerland) and associated Spiroware software (version 3.1.6). Patients performed the test seated using a noseclip and low dead space snorkel-like mouthpiece (EcoMedics). At each visit patients aimed to achieve three acceptable trials according to ERS/ATS consensus criteria and underwent qualitative quality control assessment (12).

**The Pittsburgh Sleep Quality Index (PSQI)**

The PSQI was used for both an initial assessment and ongoing comparative measurements in enrolled patients across the health care continuum (10).
Data analysis

Data were statistically analyzed using the SPSS software (version 15.0) and presented as mean ± standard deviation (SD). Shapiro-Wilk normality test was used to assess data distribution patterns. QQ-plots and attendant regression were adopted (13). The non-parametric Mann-Whitney test was used in addition to the Pearson’s correlation coefficient. A p value < 0.05 was considered statistically significant. Fit was assessed in each model using the associated R^2 and P values.

Results

All 6 patients (male:female 2:4, mean age ± SD: 23.3±5.8) completed the study with full satisfaction. All patients had a good adherence to the treatment and no adverse effect was reported.

Demographic and functional data at baseline (day 1) and at the end of the study (year 1) are shown in table 1.

Effects of NIV on clinical and laboratory findings

The mean pressures used for NIV were IPAP 10 cmH20 and EPAP 5 cmH20 in spontaneous/controlled mode. NIV significantly reduced the nocturnal respiratory rate (28.4±4.2 vs. 23.5±1.9, p<0.01) and improved mean nocturnal SaO2% (91±1.0 vs. 94±1.0, p<0.001).

The mean number of exacerbations was 4.7 in the pre-treatment year and 2.2 during the treatment year (p<0.001).

PaO2 and PaCO2 also remained stable after one year (Table 1).

NIV and lung function tests

After one year of nocturnal NIV polysomnographic parameters showed a significant improvement detected in mean nocturnal SpO2 and SpO2 <90% values (table 1).

The FEV1% values were stable after one year, whereas the LCI values decreased by 12% but not significantly (from 17.4 to 15.5; p: n.s).

NIV and PSQI

After one year of nocturnal NIV, a significant improvement in PSQI was also recorded (17.1±2.1 vs.13.5±2.1; p<0.05).

Discussion

In our pilot study nocturnal NIV treatment appeared a preventive and useful therapeutic strategy to reduce the number exacerbation/year and polysomnographic parameters, as well as quality of life in normoxic and normocapnic awake patients with CF.

Infectious exacerbations play an important role in the progressive loss of functional lung tissue and in the disease’s progression, and predictive biomarkers for clinical decay are not still available (20, 21-25). Although pursuing a reduction in the number of exacerbations is pivotal, no study conducted on patients with CF in treatment with NIV has clearly addressed this outcome (1). In light of the evidence that the use

| Table 1. Demographic, clinical, biochemical, and instrumental findings of the enrolled patients at baseline (day 1) and at the end of the study (year 1). |
|--------------------------------------------------|
| Patients                                         |
| Demographic findings                            |
| Number patients                                  | 6 |
| Gender (M:F)                                     | 2:4 |
| Age (years)                                      | 23.3±5.8 |
| Clinical and biochemical findings                |
| Exacerbations/year                               | 4.7±1.1  | 2.0±0.5  | <0.001 |
| \[^{*RR}\]Pao\(_{2}\)\(\text{mmHg}\)               | 83.3±2.9  | 80.5±7.5  | n.s. |
| \[^{*PaCO}_{2}\]\(\text{mmHg}\)                   | 41.8±2.2  | 39.0±2.1  | n.s. |
| Awake \[^{*SpO}_{2}\] (%)                         | 96±0.8    | 96±0.4    | n.s. |
| Awake respiratory rate                           | 22±2.0    | 22±1.1    | n.s. |
| Lung function tests                              |
| \[^{*FEV}_{1}\]%                                 | 39.9±12   | 39.3±10   | n.s. |
| \[^{*LCI}\]                                  | 17.4±0.41 | 15.5±0.82 | n.s. |
| \[^{*PSQI}\]                                 | 17.1±2.1  | 13.5±2.1  | 0.014 |
| \[^{N.s.}\]: not significant; lci: lung clearance index; fev1%: forced expiratory volume in 1 second; rr: respiratory rate; pao2: partial pressure of oxygen; paco2: partial pressure of carbon dioxide; tcco2: transcutaneous co; spo2: oxygen saturation; pg: poligraphy; ahi: apnea-hypopnea index; odi: oxygen desaturation index; psqi: pittsburgh sleep quality index |
of NIV is not without risk, especially in patients infected with Pseudomonas aeruginosa and/or experiencing severe airflow obstruction, to date, the use of NIV in patients with CF is limited to acute or chronic lung failure as well as a bridge to transplantation at the end stage of lung diseases (26). Firstly, we proposed an early use of NIV in stable patients with CF to evaluate a favourable relationship with clinical outcomes.

Infectious exacerbations of lung diseases in patients with CF must be recognised early and treated promptly in order to counteract lung failure. In addition to its physiological effects, NIV treatment, facilitating airway drainage all through the day, has been considered as a useful adjunct to other airway clearance techniques (27). So far, only a late treatment with NIV has been used in hypercapnic patients and associated with the slowing progression of respiratory failure, herein, we firstly proposed an early treatment with NIV and showed that, after one year of treatment, all enrolled patients reported a significant decrease in number of exacerbations/year. In parallel, polygraphic respiratory events during sleep in patients treated with home NIV appeared significantly improved; an overall decrease in respiratory events and normalization of respiratory gases were recorded. Although the positive NIV effects on nocturnal cardio-respiratory polygraphy are well known (1), to the best of our knowledge, no trials evaluated diagnostic polysomnography results after long-term NIV use. Herein, we firstly reported significant improvement in polysomnography results after 12 months NIV use and also revealing as this tool can further support the long-term NIV use in stable CF patients.

Treatment with NIV in severe CF patients has been shown to slow the lung failure in terms of FEV1 (2, 3). Accordingly, we found that the FEV1 was unchanged after one year of nocturnal NIV even in stable CF patients. Although the FEV1 has been the main outcome of most studies for many years, recently the LCI has been also used for the functional evaluation of patients with CF (4, 28). LCI reflects the degree of inhomogeneity of ventilation distribution and provides informations complimentary to FEV1, and it can be an alternative measure to high resolution computed tomography (CT) for detecting early pulmonary abnormalities (17, 18). Firstly, our study provided the evidence that a long-term NIV did not influence LCI values. The mechanism underlying the effect of NIV in CF is unclear. In patients with chronic obstructive lung disease NIV treatment reduces distal airway resistance, improves the ventilation/perfusion ratio (VQ), and recruits collapsed alveolar units via expiratory positive pressure (19); thus, it is reasonable to hypothesize that similar mechanisms can occur even in patients with CF favouring an improvement both in the ventilation distribution and VQ ratio.

Moreover, we noted that NIV treatment significantly reduced the nocturnal respiratory rate in our population, although maintaining stable nocturnal levels of TcCO2.

Even if the association between lung function and quality of life is widely described in patients with CF (27), the available studies are unable to provide data on the impact of nocturnal NIV treatment on quality of life in stable CF patients (29-31). In this regard, our study showed that nocturnal NIV treatment significantly improved quality of life and it appeared well tolerated despite the use of relatively high inspiratory pressures for a long time (12 months). We suggest that the observed improvement in health status of all enrolled patients is related to a decrease of infectious exacerbations.

Our study has some limitations. First, the sample size is small and not entirely representative of the wide spectrum of the disease in relationship to the clinical presentation and respiratory impairment, even in the presence of identical genetic mutation. It is also noteworthy that the MBW test to derive LCI, is an emerging technique to monitor the disease progression and standardized protocols in CF are still unavailable. In our studies LCI values were decreasing but not significantly, probably, a further study with a more large sample size could be useful to achieve to more sensitive information on this issue and define if LCI could as a reliable tool for an useful clinical assessment of CF. In conclusion, we believe that our preliminary data may provide the base to other larger, multicenter studies. We base this assumption on the following novel findings: 1) the use of preventive nocturnal NIV in normoxemic and normocapnic awake CF has never been explored; 2) the nocturnal NIV seems to be beneficial because it has been able to prevent the number of ex-
acerbations/year and the effect on nocturnal cardio-respiratory polygraphic values is a further element explaining usefulness of NIV treatment in CF; 3) the nocturnal NIV treatment significantly improved quality of life and it appeared well tolerated despite the use of relatively high inspiratory pressures for a long time.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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