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Original Research Article

Our ICU experience with non-invasive ventilation for acute exacerbations in adults with cystic fibrosis

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Abstract

We report our experience of using noninvasive ventilation (NIV) in 15 adult cystic fibrosis (CF) patients with chronic respiratory failure, admitted in intensive care unit (ICU) during episodes of acute infectious exacerbation. The mean age of the patients was 28.73 ± 5.66 years, 8 males and 7 females.Prior to ICU admission, all patients had had FEV_1<51%. Oxygen saturation on room air was 83,5%±4.5 with PCO2 raging from 4.2 to 6.59 kPa. At admission all were initially treated with NIV to avoid adverse effects of tracheal intubation, none of the patient required intubation. We used NIV-BiPAP mode with 40% of oxygen, aiming to maintain stable hemodynamic in all patients. Settings were adjusted to arterial blood gas values. Once the SatO2 was stable 90% or over and PCO2 ranged from 4 to 5.29kPa the NIV was stopped in all but one patient. Length of stay in ICU was 13,13±5,35 days. All patients were discharged alive from the ICU. In the follow up a year after discharge we recorded 1 death, 4 patients included in lung-transplant waiting list, 3 patients in a process for lung transplant evaluation and the rest of the patients hadn't required re-admissions in ICU. Our results confirm the published data that NIV can serve as a bridge towards lung transplantation for CF patients with end-stage lung disease and not merely prolonging the suffering. NIV improved hypoxia and fairly corrected hypercapnia in our patients. For these patients, there is a possibility of prolonging life if they are successfully treated for their acute episode of respiratory failure until transplantation.

Key words: End-stage lung disease, cystic fibrosis, NIV

INTRODUCTION

Cystic fibrosis (CF) is a complex, autosomal-recessive disorder, affecting the functions of respiratory system, gastro-intestinal tract and all exocrine glands (O'Sullivan and Freedman, 2009). The disease is a result of a mutation in the gene for cystic fibrosis transmembrane conductance regulator (CFTR). The chronic infections and inflammation, leading to bronchiectasis and respiratory failure are the leading cause for morbidity and mortality. The incidence of CF varies in different races and ethnicity. For Europe average incidence is 1:2500 newborns, in Bulgaria is around 1:3600,while in Ireland is higher up to - 1:800 (Kremensky, 2006; Elborn, 2013). In the last decades survival of CF patients has been drastically improved due to newer therapeutically regimens, with the last two years both USA and European registries report over 50% of adults (Cystic Fibrosis Foundation, 2016; European Cystic Fibrosis Society Patient Registry Annual Data Report (2014). If this tendency persists in the next years we could predict that in 2040 CF patients would have life expectancy of 70 years (Simmonds et al., 2009). The factors contributing this abrupt prolongation include inhaled antibiotics, better nutrition, earlier diagnosis (Elborn, 2013).

Nevertheless the decision to admit adult patients with

CF in intensive care unit (ICU) is still controversial, mostly because of futility reasons (Davis and di Sant'Agnese, 1978). Non-invasive ventilation (NIV) may be a means to temporarily reverse or slow the progression of respiratory failure in CF by providing ventilatory support and avoiding tracheal intubation. Using NIV, in the appropriate situation or individuals, can improve lung mechanics through increasing airflow and gas exchange and decreasing the work of breathing (Moran et al., 2013). In the last two decades form multiple retrospective analyses of the ICU mortality rate for admitted adults with CF showed drop to 18% (Texereau et al., 2006). The numbers are close to the average overall ICU mortality rate reported in the US ranges from 8% to 19% (Mukhopadhyay et al., 2014). This decrease in adult CF mortality rate may partially result from the significant increase in NIV use in the ICU management of CF patients, despite the absence of evidence-based guidelines.

In Bulgaria from roughly 220 CF patients (Petrova et al., 2016) about 43% are adults, most of them with advanced lung involvement and frequent pulmonary exacerbations. Sincewe still don't have specialized CF centers the treatment of adult CF patients is still a challenge for us.

The aim of our study was to describe our experience in managing with NIV for CF adults with pulmonary exacerbations admitted in ICU in the last 2 years.

MATERIAL AND METHOD

We included 15 patients with advanced lung disease with a genetically and clinically proven CF (mean age 28.73 ± 5.66 years), 8 males and 7 females. All patients are followed since the diagnosis for a long term in the University Hospital "Alexandrovska". Exacerbations were defined by acute changes in respiratory signs and symptoms, such as: fever for more than 3 days, increased cough frequency and sputum production, weight loss, new auscultation findings (crackles, wheezing, rales or ronchi), inflammation changes according to the complete blood count (elevated leucocytes, erythrocyte sedimentation rate and C-reactive protein), new changes on X-ray, the drop of functional vital capacity (FVC), forced expiratory volume for 1 second (FEV1) and $SatO_2$.

The following data were collected by reviewing patient medical charts: CFTR genotype, extra-pulmonary manifestations of CF and features of airway chronic bacterial colonization. The severity of respiratory functional impairment was assessed by using the best baseline lung function test performed during a stable outpatient visit within the 6 months preceding ICU admission. Body mass index (BMI) was used as a marker of nutritional state. CFTR genotypes were grouped into severity classes according to the probable functional consequences on CFTR protein: "mild" for patients with at least one mutation of classes IV or V; "severe" for patients with two mutations of classes I, II or III; and "not determined" for patients with only one identified mutation of class I, II or III (Zielenski, 2000).

Anthropometric data (height and weight) in all patients were measured with a calibrated balance and meter (Detectoscale, USA). The spirometry recorded had been performed within 2 months of the ICU admission and a year afterwards. For spirometry we used MasterscreenPneumo spirometer ' 98 (Jager ®, Wuerzburg, Germany), with drawing curves in real time and automatic correction (BTPS), in accordance with world standards by complying with the ATS/ERS criteria for repeatability and reproducibility (Laszlo, 2006). SpO_2 and heart rate were recorded using a pulse oximeter with finger probe (Onyx vantage, Nonin, USA), PO2 and PCO2 were measured in the blood through arterial blood gas analysis. The sputum microbiology results were those from samples collected during or closest to hospital admission.

The duration of ventilatory support, the length of ICU stay and patient immediate outcome were also collected, as well as the data one-year follow-up.

Statistical analysis and graphical representations, providing statistical data are made through SPSS ®, IBM 2009, version 19 (2010) Excel (v.) 2010. We used descriptive and correlation analysis.

RESULTS

Prior to ICU admission, all but three patients had a severe lung disease (with FEV1<40%), the rest 3 patients had FEV1<51%.The reason for ICU hospitalization was pulmonary infective exacerbation. Oxygen saturation on room air was 83.5%±4.5 with PCO_2 from 4.2 to 6.59 kPa. At admission all were initially treated with NIV to avoid adverse effects of tracheal intubation, none of the patient required intubation. We used NIV-BiPAP mode with 40% of oxygen, aiming to maintain stable hemodynamic in all. Settings were adjusted to arterial blood gas values. Once the $SatO_2$ was stable 90% or over and PCO_2 ranged from 4 to 5.29 the NIV was stopped in all but one patient. Length of stay in ICU was 13.13±5.35 days (range 7 to 23). All patients were discharged alive from the ICU. In the follow up of these 15 patients a year after discharge we recorded 1 death, 4 patients included in lung-transplant waiting list, 3 patients in a process for lung transplant evaluation and the rest of the patients hadn't required re-admissions in ICU. The patients' characterristics are shown on table 1.

Noninvasive ventilation (NIV) was the main ventilatory support, initiated at admission for 7.2 ± 6.5 days. No one of the 15 patients required endotracheal intubation. There were no significant correlations with the length of stay and the NIV duration with the parameters, regarded

Table 1. The characteristic of all the patients

Patient	gender	Age (y)	mutations	FEV1%	FVC%	BMI	CF-related complications	mo sputum	SatO2 (%)	LOS ICU (days)	1 year follow up
1	M	25	ΔF506/N1303K	22,97	31,63	17,99	PI, Ptx	PA	87	21	Ltx-WL
2	M	29	ΔF506/ ΔF506	14,75	17,06	17,81	PI,LD	SA	92	15	Ltx-WL
3	F	24	ΔF506/ 2184insA	22,46	26,3	13,91	PI,LD	PA	88	21	Ltx-ev.
4	F	27	ΔF506/ ΔF506	37,85	53,74	16,02	PI	PA	92	10	Ltx-ev.
5	F	33	ΔF506/ 3849+10kbC-T	38,76	46,87	19,71	HAEM BD	BC	90	14	stable
6	F	33	R1070Q/ 2184insA	46,86	50,64	16,53	PI,LD,DM	PA	89	7	stable
7	F	27	ΔF506/ ΔF506	40,27	68,78	19,95	PI,LD	PA	88	10	stable
8	M	27	ΔF506/N1303K	42,16	54,91	17,22	PI,LD,BD	PA	93	13	stable
9	F	19	ΔF506/ ΔF506	32,37	44,4	13,71	PI,LD	PA	90	12	Ltx-ev.
10	M	43	ΔF506/ unknown	51,03	81,93	20,2	PI	SA	89	7	stable
11	M	29	ΔF506/ 1898+3A->G	38,18	50,89	20,72	PI	PA	93	8	stable
12	M	34	ΔF506/ ΔF506	47,17	56,75	19,03	PI	PA	88	7	stable
13	M	23	ΔF506/ ΔF506	26,47	31,82	16,53	PI,LD	PA	88	12	Ltx-WL
14	M	31	ΔF506/G1069R	16,51	35,27	15,63	PI,DM	PA	86	23	Ltx-WL
15	F	27	Q220X/2183AA ->G	33,49	40,94	18,9	PI,LD,DM	PA	90	17	dead
mean				34.08±11.28	46.12±16.63	17.59±2.02			89±2.3	13,13±5,35	

F, female; M, male; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; PI, pancreatic insufficiency; DM, diabetes mellitus; LD, liver disease; HAEM, haemoptysis; PTX, pneumothorax; BD, bone disease; MO, micro-organism; PA, Pseudomonas aeruginosa; BC, BurkholderiaCepacia; SA, staphylococcus aureus; LOS ICU, length of stay in intensive care unit; LTX, lung transplantation; WL – waiting list; ev – evaluation

Table 2. Summary statistic for all alive patients one year after ICU discharge

Age, yr	29.85 ± 5.85
Alive/dead	14/1
Sex, M/F	8/6
Severity of *CFTR* genotype, S/M/ND	11/3/1
BMI, Kg/m^2	17.3± 2.25
Extra-pulmonary involvement	
Pancreatic insufficiency	13 (92%)
Diabetes	2 (15%)
Liver disease	7 (50%)
Chronic airway colonization	
P. aeruginosa	11 (78%)
B. cepacia complex	1 (7%)
Lung function in stable state	
FEV_1, % predicted	38,10 ± 17,6

Table 2. Continue

FVC, % predicted	50,27 ± 21,34
Room air SaO_2, %	89 ± 8
Home ventilatory support	
Long term oxygenotherapy alone	4 (28%)
Non-invasive ventilation	1 (7%)
Patients awaiting lung transplant	4 (28%)

Values are expressed in mean ± SD or number (percentage of the alive patients).
M: male; F: female; CFTR: cystic fibrosis transmembrane conductance regulator; S: severe; M: mild; ND: not determined; BMI: body mass index; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; SaO_2: arterial oxygen saturation
Due to the high cost of the NIV system, only one patient has NIV at home for long term therapy.

for the severity of the disease such as CFTR genotype, lung function tests, airway bacterial colonization, gender and age. Summary statistic on data from one-year follow-up is shown on table 2

DISCUSSION

We usually relate the severity of CF lung-disease to several key parameters such as the mutationsclass, spirometry results, airway bacterial colonization, gender and age (Kerem et al., 1992; Liou et al., 2001; Aurora et al., 2000; Hayllar et al., 1997). According our results none of these recognized prognostic factors were associated with the ICU outcome.

Decision to admit adult patients with CF in ICU is still controversial, mostly because of futility reasons. Our data support more recent publications that the survival rate of adult patients admitted to ICU with respiratory deteriorations has improved when compared to 30 years ago (Davis and di Sant'Agnese, 1978). All but one patients admitted to ICU in our study survived to hospital discharge and twelve months following discharge.

Almost 10 years ago a French survey of NIV use in over 4000 patients with CF showed that NIV is used as a first-line treatment for severe hypercapnic respiratory exacerbation and for stable diurnal hypercapnia, especially when associated with sleep disturbances. The suggested ventilation mode is Bi-level, pressure-targeted ventilation (Fauroux et al., 2008). Following these data in a multicenter study Texereau et al. have shown that NIV is the main ventilatory support, used in 73% of pulmonary infective exacerbations in adult CF patients. In the same study it was revealed that patients with successful NIV, defined by ICU discharge without endotracheal intubation, had a more severe basal lung function than patients requiring intubation. NIV success was more frequent among patients with prior home NIV, suggesting the importance of education and chronic respiratory management (Texereau et al., 2006).

CF patients with end-stage lung disease required ICU treatment should not be excluded from lung transplants waiting lists. In the aforementioned study the authors concluded also that 1/3 of their patients underwent lung transplantation within 6 months after ICU hospitalization. Similarly Sood et al. reported data for successful lung transplantation in more than 60% of ICU survivors within 1 year after discharge (Sood et al., 2001). Furthermore it was previously confirmed, that acute episodes requiring intravenous therapy did not adversely affect the one-year survival benefit after lung transplantation (Bartz et al., 2003). NIV has been used successfully as a bridge to transplantation in patients with cystic fibrosis where invasive ventilation produces a uniformly poor outcome (Hodson et al., 1991). In a retrospective review Madden et al. found that particularly in patients who have been accepted, or are being evaluated for lung transplantation, NIV offers the possibility of prolonging survival until transplantation can occur (Madden et al., 2002).

Therefore, hospitalization of such patients in ICU may be justified by both the possibility to adapt chronic management (like implementing home ventilatory support) and the chance for surviving through lung transplantation.

NIV failure leading to endotracheal intubation and is associated with a very poor outcome, confirming that prognosis of intubated CF patients has not improved during the last thirty years (Texereau et al., 2006).

There are no randomized controlled trials of NIV versus conventional treatment in CF patients. Physiologically, they are similar to patients with COPD with evidence of severe airflow obstruction. However, in addition, secretions are often excessive and this may limit the applicability of NIV (Hodson et al., 1991). Holland et al. have shown that NIV can safely be used to assist airway clearance during acute exacerbations in adults with CF, and that beneficial effects may be seen in those with severe bronchial obstruction and reduced inspiratory muscle strength (Holland et al., 2003). Combining all available data and her own studies in 2016 Hortal published a thesis showing that NIV may be applied safely to respiratory diseases involving affected mucociliary clearance, and as assisted-exercise to compensate for the ventilaroty limitations. The studied

population of CF patients, of which 64 % were adults, displayed good lung function; nevertheless these patient characteristics should also be applicable to other countries (Hortal MCR, 2016).

There are some limits to this study. Our study relied on observational data, rather than on the results of a prospective trial, the potential for patient selection bias, although small, remains. In Bulgaria there are no specialized CF centers, which pose a lot of problems when dealing with specific requirements of these patients. It is well known fact that CF patients benefit from regular and standardized medical care in specialized centers that allow precise evaluation of their clinical characteristics at ICU admission and a complete reliable long-term follow-up. There is absence of well-defined ICU admission criteria but a recent French study has shown that CF patients with pulmonary exacerbations admitted in ICU were significantly more severe than those treated in the pulmonary ward of the same hospital (Ellaffi et al., 2005), underlying that request for ICU admission is mainly triggered by clinical instability, the need for close monitoring or the probability for endotracheal intubation.

CONCLUSION

Despite the admission of older CF patients with advanced lung disease the overall mortality of those hospitalized in ICU decreases in recent years. Decision to admit these patients in ICU should not be regarded as bad prognostic factor and it should not compromise the opportunity for lung transplantation. The use of NIV should be strongly recommended. A protocol and adefinition of appropriate ICU admission criteria for these patients is vital. The biomarkers used to assess severity of chronic pulmonary disease are poor predictors for ICU outcome and future studies focusing on more relevant parameters are needed.

REFERENCES

Aurora P, Wade A, Whitmore P, Whitehead B (2000). A model for predicting life expectancy of children with cystic fibrosis. EurRespir J, 16:1056-60.

Bartz RR, Love RB, Leverson GE, Will LR, Welter DL, Meyer KC (2003). Pre-transplant mechanical ventilation and outcome in patients with cystic fibrosis. J Heart Lung Transplant,22:433-8.

Cystic Fibrosis Foundation (2016). Patient Registry 2015 Annual Report. Bethesda, Maryland. Cystic Fibrosis Foundation

Davis PB, di Sant'Agnese PA (1978). Assisted ventilation for patients with cystic fibrosis. Jama, 239:1851–4.

Elborn S (2013). Cystic fibrosis, ERS lung white book

Ellaffi M, Vinsonneau C, Coste J, Hubert D, Burgel PR, Dhainaut JF, Dusser D (2005). One-year outcome after severe pulmonary exacerbation in adults with cystic fibrosis. Am J RespirCrit Care Med;171(2):158-164.

European Cystic Fibrosis Society Patient Registry Annual Data Report (2014)

Fauroux B, Burgel PR, Boelle PY, Cracowski C, Murris-Espin M, Nove-Josserand R, Stremler N, Derlich L, Giovanetti P, Clément A; Chronic Respiratory Insufficiency Group of the French National Cystic Fibrosis Federation. (2008). Practice of noninvasive ventilation for cystic fibrosis: a nationwide survey in France. Respir Care;53:1482–9

Hayllar KM, Williams SG, Wise AE, Pouria S, Lombard M, Hodson ME, Westaby D (1997). A prognostic model for the prediction of survival in cystic fibrosis. Thorax, 52:313-7.

Hodson ME, Madden BP, Steven MH, Tsang VT, Yacoub MH (1991). Non-invasive mechanical ventilation for cystic fibrosis patients–a potential bridge to transplantation. EurRespir J;4:524–7.

Holland A, Denehy L, Ntoumenopoulos G, Naughton M, Wilson J (2003). Non-invasive ventilation assists chest physiotherapy in adults with acute exacerbations of cystic fibrosis. *Thorax.*;58(10):880-884. doi:10.1136/thorax.58.10.880.

Hortal MCR (2016). Non invasive ventilation in people with cystic fibrosis, doctoral thesisKarolinskaInstitutet,

Kerem E, Reisman J, Corey M, Canny GJ, Levison H (1992). Prediction of mortality in patients with cystic fibrosis. N Engl J Med, 326:1187-91.

Kremensky I (2006). Cystic fibrosis, doctoral thesis, Medical University Sofia, Bulgaria (in Bulgarian)

Laszlo G (2006). Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. Thorax.;61(9):744-746.

Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC (2001). Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol, 153:345-52.

Madden BP, Kariyawasam H, Siddiqi AJ, Machin A, Pryor JA, Hodson ME (2002). Non-invasive ventilation in cystic fibrosis patients with acute or chronic respiratory failure. EurRespir J;19(2):310 –3.

Moran F, Bradley JM, Piper AJ (2013). Non-invasive ventilation for cystic fibrosis. Cochrane Database of Systematic Reviews, Issue 4. Art. No.: CD002769. DOI: 10.1002/14651858.CD002769.pub4. (updated 2017)

Mukhopadhyay A, Tai BC, See KC, Ng WY, Lim TK, Onsiong S, Ee S, Chua MJ, Lee PR, Loh ML, Phua J (2014). Risk factors for hospital and long-term mortality of critically ill elderly patients admitted to an intensive care unit. Biomed Res Int.; 2014:960575

O'Sullivan BP, Freedman SD (2009). Cystic fibrosis. Lancet; 373: 1891–1904

Petrova G, Yaneva N, Kalcheva M, Alexiev A, Mihova R, Atanasova S, MinchevaTs, Georgieva A, Strateva T, Savov A (2016). Pilot data from the bulgarian cystic fibrosis registry. Rare dis and orphan drugs;7(3):11-16 (in Bulgarian)

Simmonds NJ, Cullinan P, Hodson ME (2009). Growing old with cystic fibrosis—the characteristics of long-term survivors of cystic fibrosis. Respir Med; 103: 629–35.

Sood N, Paradowski LJ, Yankaskas JR (2001). Outcomes of intensive care unit care in adults with cystic fibrosis. Am J RespirCrit Care Med;163(2):335-338.

Texereau J, Jamal D, Choukroun G, Burgel PR, Diehl JL, Rabbat A, Loirat P, Parrot A, Duguet A, Coste J, Dusser D, Hubert D, Mira JP. (2006). Determinants of mortality for adults with cystic fibrosis admitted in Intensive Care Unit: a multicenter study. Respiratory Research.;7(1):14.

Zielenski J (2000). Genotype and phenotype in cystic fibrosis. Respiration 67:117–33.