Noninvasive Ventilation in Cystic Fibrosis: Clinical Indications and Outcomes in a Large UK Adult Cystic Fibrosis Center

Giulia Spoletini, Kim Pollard, Ruth Watson, Michael J Darby, Annette Johnstone, Christine Etherington, Paul Whitaker, Ian J Clifton, and Daniel G Peckham

BACKGROUND: Noninvasive ventilation (NIV) is routinely used to treat patients with cystic fibrosis and respiratory failure. However, evidence on its use is limited, with no data on its role in disease progression and outcomes. The aim of this study was to assess the indications of NIV use and to describe the outcomes associated with NIV in adults with cystic fibrosis in a large adult tertiary center. METHODS: A retrospective analysis of data captured prospectively on the unit electronic patient records was performed. All patients with cystic fibrosis who received NIV over a 10-y period were included in the study. A priori, 2 groups were identified based on length of follow-up, with 2 subgroups identified based on duration of NIV treatment. RESULTS: NIV was initiated on 64 occasions. The duration of follow-up was categorized as > 6 months or < 6 months in 31 (48.4%) and 33 (51.6%) occasions, respectively. The most common indications for starting NIV were chronic (48.5%) and acute (32.8%) hypercapnic respiratory failure. Among those with a follow-up > 6 months, subjects who stopped using NIV early showed a steady median (interquartile range) decline in FEV_1 (pre-NIV: –0.04 [–0.35 to 0.03] L/y vs post-NIV: –0.07 [–0.35 to 0.01] L/y, $P = .51$), while among those who continued using it had an improvement in the rate of decline (pre-NIV: –0.25 [–0.52 to –0.02] L/y vs post-NIV: –0.07 [–0.13 to 0.16] L/y, $P = .006$). No differences in intravenous antibiotic requirement or pulmonary exacerbations were noted with the use of NIV. Pneumothorax and massive hemoptysis occurred independently in 4 cases. CONCLUSIONS: NIV is being used in cystic fibrosis as adjunct therapy for the management of advanced lung disease in a similar fashion to other chronic respiratory conditions. Adherence to NIV treatment can stabilize lung function but does not reduce pulmonary exacerbations or intravenous antibiotic requirement. *Key words: cystic fibrosis; respiratory failure; noninvasive ventilation; lung function decline; pulmonary exacerbations.* [Respir Care 2021;66(3):466–474. © 2021 Daedalus Enterprises]

Introduction

Cystic fibrosis (CF) is one of the most common autosomal recessive life-limiting genetic disorders in the caucasian population.[1] Despite being a multi-system condition, morbidity, mortality, and hospitalizations in patients with CF are most frequently secondary to respiratory complications. Lung involvement is characterized by chronic endobronchial infection, recurrent pulmonary exacerbations, airway inflammation, and progressive lung damage, with small and large airways disease, air trapping, hyperinflation, and bronchiectasis.[1,2]

The introduction of new therapies in combination with high-quality multidisciplinary care has resulted in significant improvement in the quality of life and survival of individuals with CF.[3,4] Despite these changes, approximately 20% of individuals develop severe lung disease by the age of 30.[3] This progression in lung disease results in abnormal gas exchange, with nocturnal hypoxemia and hypercapnia often

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preceding daytime respiratory failure.[2] Chronic respiratory failure is associated with a poorer outcome and a more rapid decline in lung function, and it is an indication for referral for lung transplantation.[5,6] By slowing the rate of progression of respiratory failure, contributing to control of inflammation, and favoring expectoration (thereby reducing the risk of atelectasis), noninvasive ventilation (NIV) has the potential to improve prognosis in individuals with CF.[7,8] In addition, NIV is used where appropriate to treat acute respiratory failure during episodes of pulmonary exacerbations.

The mainstay therapeutic approaches to respiratory failure include treatment optimization of the underlying condition in combination with appropriate respiratory support. In CF, respiratory failure is often the result of disease progression, with many patients on appropriate treatment regimens at the time of presentation. In this context, oxygen therapy and NIV are the most common methods of respiratory support used. A recent Cochrane review concluded that long-term oxygen therapy does not improve survival in CF, and that treatment overnight can lead to marginal increase in carbon dioxide.[9] Similarly, evidence on the role of NIV is limited, with no data on the impact of this treatment modality on disease progression.[7] Despite the lack of evidence, both oxygen therapy and NIV are used routinely in everyday clinical practice. Between 5% and 10% of patients with CF receive NIV at least once in their life, despite the lack of validated criteria for initiation and termination of treatment.[10-13]

The aim of this study was to assess the indications of NIV use in adults with CF attending a large regional referral center and to describe the outcomes associated with this treatment.

QUICK LOOK

Current knowledge

Approximately 20% of people with cystic fibrosis develop severe lung disease by the age of 30. Invasive mechanical ventilation is associated with poor outcomes in patients with cystic fibrosis and severe lung disease. Noninvasive ventilation (NIV) is routinely used in clinical practice to treat patients with cystic fibrosis and severe lung disease, despite scarce evidence on its use in this population.

What this paper contributes to our knowledge

NIV was used in subjects with cystic fibrosis in a similar fashion to other respiratory conditions and was not associated with significant complications. Use of NIV appeared to stabilize lung function in subjects with advanced lung disease but did not affect pulmonary exacerbation rate. Adherence to NIV, airway clearance therapy, and baseline treatment needs to be considered.

Methods

Study Design

We performed a retrospective analysis of data captured prospectively on the electronic medical records of the Leeds Regional Adult Cystic Fibrosis Centre. All patients had previously consented for their clinical data to be used for research purposes. The study was approved by the local Research and Innovation Department (RM17/99996).

Subjects

Inclusion criteria were age ≥ 17 y, having a confirmed diagnosis of CF, and having received ≥ 12 h of NIV between January 2008 and December 2018. Individuals who had NIV after lung transplant or specifically for chest physiotherapy and those who were treated with CPAP due to obstructive sleep apnea were excluded from the study. To assess the medium-term outcomes of treatment with NIV, 2 groups were identified a priori based on the length of follow-up with the CF Unit (≥ 6 months and < 6 months). Among subjects with ≥ 6 months follow-up, 2 subgroups were identified based on the duration of NIV treatment. The first subgroup included those subjects who remained on NIV throughout their follow-up period, while the second included those who declined to continue NIV treatment (early termination) because of discomfort despite continued clinical and blood gas indications for NIV. Subjects were considered part of the study during their follow-up with the CF unit, or until December 2019, depending on which occurred earlier.

Data Collection

A search of the electronic patient record identified all subjects meeting the eligibility criteria. Baseline demographics, comorbidities, and microbiology status at the time of starting NIV were recorded, as well as date when

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The authors have disclosed no conflicts of interest.

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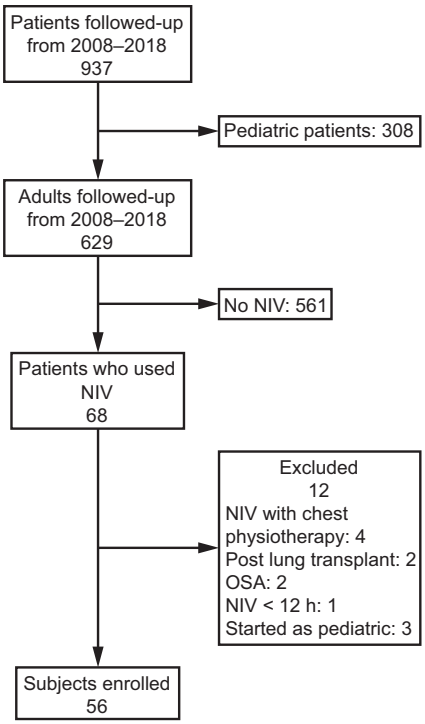

Fig. 1. Flow chart. NIV = noninvasive ventilation; OSA = obstructive sleep apnea.

treatment with NIV was discontinued, date of transplant, and death. Lung transplant status was also recorded (ie, subject on the active transplant list, under consideration for transplantation at a transplant referral center, not yet referred, or unsuitable candidate for transplantation).

Computed tomography scans performed within 12 months of NIV start date were also retrieved and independently reviewed by 2 chest radiologists according to the modified Bhalla score.[14] All available measurements of lung function in the 12 months before and after starting NIV were retrieved. From these measures, highest and lowest FEV_1, $FEF_{25-75\%}$, and FVC were extrapolated. FEV_1 decline was computed through linear regression in the year before and in the year after start of NIV. Duration of intravenous antibiotics and length of in-hospital stay were retrieved for the year before and after the start of NIV. Electronic medical notes were individually reviewed to record symptoms at start of NIV treatment, annotations of self-reported side effects, and complications of NIV.

Statistical Analysis

Comparison of variables before and after NIV were performed with paired *t* tests for normally distributed data and with Wilcoxon signed rank tests if data were not distributed normally. Unpaired *t* tests or Mann-Whitney tests were used for between-group comparisons of normally and non-normally distributed data, respectively. The chi-square test was used to assess differences in frequency distributions between groups. Data were reported as mean ± SD if normally distributed and as median (interquartile range [IQR]) if not. All statistical tests were 2-sided, and the significance level was set at $P < .05$. SPSS 23 (IBM, Armonk, New York) was used for the analyses.

Results

Subjects

Over the study period, 68 of 629 adults with CF were treated with NIV on at least one occasion. Eligibility criteria were met in 56 cases (Fig. 1), with NIV being initiated on 64 occasions and with 7 subjects receiving NIV more than once. Four subjects who recovered from a first episode of acute hypercapnic respiratory failure presented again with acute or chronic respiratory failure. Three subjects declined to continue with NIV but retried it during a subsequent admission.

Table 1 summarizes the baseline characteristics of subjects at the time of starting NIV. In 31 (48.4%) instances of NIV initiation, subjects were followed up for > 6 months. In the remaining 33 (51.6%) occurrences, follow-up was < 6 months. Groups were similar for demographics, comorbidities, and microbiology. However, lung function tended to be lower among subjects with shorter follow-up; they required more intravenous antibiotic treatment in the year preceding the start of NIV treatment, and they appeared to be on long-term oxygen therapy more often. More subjects in the short follow-up group were on the active transplant waiting list or under consideration for lung transplantation (Table 1). No differences in the radiological patterns according to the Bhalla score were observed between the 2 groups.

NIV Courses

NIV was started during a hospital stay in all but 1 case. Symptoms suggestive of carbon dioxide retention, such as morning headaches, lethargy, and drowsiness or dyspnea, and signs of increased work of breathing (tachypnea and use of accessory muscle) were assessed on admission and daily. Blood gas analyses were performed in the presence of such symptoms or signs, and NIV was started accordingly.

Chronic type II respiratory failure was the most common indication to start NIV (31 of 64, 48.5%), followed by acute hypercapnic respiratory failure (21 of 64, 32.8%). Other indications to start NIV treatment were symptomatic nocturnal hypoventilation (4 of 64, 6.25%), hypoxemia (5 of 64, 7.8%), and increased work of breathing (3 of 64, 4.7%). At initiation of NIV, most subjects complained of increased dyspnea (67.2%) and morning headaches (64.1%). Table 2 summarizes the distribution of symptoms, results of

Table 1. Baseline Characteristics of Subjects

	All	Follow-Up		*P*
		> 6 months	< 6 months	
Subjects	56 (100)	28	33	
NIV episodes	64 (100)	31 (48.4)	33 (51.6)	
Age at start	28.8 (24.1–34.9)	28.3 (24.4–33)	29.3 (24–34.7)	.66
Male	25 (44.6)	14 (50)	15 (45.5)	.72
FEV_1, %				
Best in the 12 months	29.5 (23–35.7)	30 (27–39.5)	29 (23–35)	.52
Lowest in the 12 months	17.0 (14–20)	17 (14–21.5)	17 (13.7–20)	.44
FEV_1 slope prior to NIV	NA	–0.16 (–0.47 to 0)	–0.18 (–0.21 to –0.15)	.92
FVC, %				
Best in the 12 months	NA	57 (42.5–66)	54.5 (46–61)	.79
Lowest in the 12 months	NA	30 (24–39.5)	30 (23–35)	.45
$FEF_{25-75\%}$, L/s				
Best in the 12 months	NA	0.46 (0.33–0.68)	0.41 (0.28–0.61)	.18
Lowest in the 12 months	NA	0.22 (0.16–0.26)	0.19 (0.16–0.25)	.43
Transplant				.02
Active list	15 (26.8)	4 (14.3)	12 (36.4)	
Under assessment	22 (39.3)	9 (32.1)	15 (45.5)	
Not yet considered	17 (30.4)	14 (50)	5 (15.2)	
Rejected	2 (3.6)	1 (3.6)	1 (3)	
Genotype				.16
F508/F508	35 (62.5)	14 (50)	24 (72.7)	
F508/del	18 (32.1)	11 (39.3)	8 (24.2)	
Other	3 (5.4)	3 (10.7)	1 (3)	
Comorbidities				
Diabetes	26 (46.4)	12 (42.9)	17 (51.5)	.45
Liver disease	36 (64.3)	20 (71.4)	20 (60.6)	.63
Sinus disease	6 (10.7)	3 (10.7)	4 (12.1)	> .99
Previous pneumothorax	9 (16.1)	3 (10.7)	6 (18.2)	.49
Previous hemoptysis	6 (10.7)	1 (3.6)	5 (15.2)	.21
Microbiology status				
P. aeruginosa	46 (82.1)	23 (82.1)	28 (84.8)	.78
A. xylosoxidans	4 (7.1)	1 (3.6)	3 (9.1)	.62
B. cepacia complex	5 (8.9)	2 (7.1)	3 (9.1)	> .99
S. maltophilia	10 (17.9)	4 (14.3)	7 (21.2)	.48
Nontuberculous mycobacterial	4 (7.1)	3 (10.7)	1 (3)	.33
Long-term oxygen therapy	10 (17.9)	3 (10.7)	10 (30.3)	.12
Duration of invasive ventilation, d	98 (51–174)	72 (41.5–124)	112 (71–265)	.01
Length of hospital stay, d	45 (25–74)	43 (14–73)	57 (33–96.5)	.11

Data are presented as *n* (%) or median (interquartile range).
NIV = noninvasive ventilation
$FEF_{25-75\%}$ = forced expiratory flow at 25% to 75% of forced vital capacity

baseline arterial blood gases, and inflammatory markers on admission, depending on the indication for initiation of NIV. Arterial carbon dioxide and pH were significantly different depending on the indication to commence NIV. Headaches, lethargy, and drowsiness were most common among those subjects who commenced NIV due to acute or chronic hypercapnic respiratory failure.

The interval time between admission and initiation of NIV treatment was variable: < 12 h in 11 cases (17.2%), 12–24 h in 12 cases (18.8%), and > 24 h [median 6.5 (IQR 1.5–88) d] in 40 cases (62.5%). No differences were observed in the interval time to start NIV depending on the indication for treatment. However, subjects who had a follow-up > 6 months were started on NIV earlier during their admission compared to those who had a shorter follow-up ($P = .004$).

NIV Setting

NIV was set either in pressure control or pressure support mode. Median inspiratory positive airway pressure at start

Table 2. Indications to Start NIV

	AHRF	CHRF	Hypoventilation	Hypoxemia	WOB	*P*
NIV episodes	21	31	4	5	3	
Male sex	9 (42.9)	17 (54.8)	1 (25)	2 (40)	1 (33.3)	.73
Age at start	29.6 (24.0–37.4)	29.5 (23.4–34.4)	29.3 (22.3–40)	22.4 (20.1–27.4)	27.6 (27–29.6)	.25
Baseline arterial blood gases						
pH	7.31 (7.28–7.33)	7.39 (7.37–7.45)	7.44 (7.43–7.52)	7.53 (7.47–7.58)	7.49 (7.40–7.54)	< .001
P_{CO_2}	9.5 (8.1–11.1)	8.47 (7.77–9.26)	7.23 (5.14–8.28)	5.89 (5.22–8.32)	6.18 (6.0–6.2)	.001
P_{O_2}	8.1 (6.9–9.7)	8.2 (7.4–8.85)	7.84 (7.3–8.1)	7.6 (6.65–7.95)	10.3 (9.6–11)	.08
HCO_3^-	30.3 (27.3–35)	38.9 (32–43.7)	43 (25.4–45.1)	36.1 (29–58.8)	36 (29–39.2)	.08
Headaches	14 (66.7)	22 (71)	4 (100)	1 (20)	0 (0)	.006
Dyspnea	14 (66.7)	20 (64.5)	2 (50)	5 (100)	2 (66.7)	.33
Sleep disturbances	3 (14.3)	13 (41.9)	4 (100)	1 (20)	0 (0)	.031
Lethargy/drowsiness	9 (42.9)	10 (32.3)	0 (0)	2 (40)	1 (33.3)	.39
Increased WOB	7 (33.3)	13 (41.9)	0 (0)	4 (80)	3 (100)	.01
C-reactive protein*	82 (29–147)	61.5 (46.3–107.5)	23.5 (15–28.5)	176 (84.5–288.5)	149 (34–232)	.02
Standard HCO_3^-	36.5 (32.2–39)	36 (33–39)	30.5 (26.7–38.7)	37.5 (27–47.25)	31 (30–32)	.39

Data are presented as *n* (%) or median (interquartile range).
* Normal C-reactive protein value < 5 mg/L.
NIV = noninvasive ventilation; AHRF = acute hypercapnic respiratory failure; CHRF = chronic hypercapnic respiratory failure; WOB = work of breathing

Table 3. NIV Settings

	Follow-Up		*P*
	> 6 months	< 6 months	
Inspiratory positive airway pressure initial, cm H_2O	15 (12–16)	14 (11–16)	.39
Inspiratory positive airway pressure final, cm H_2O	20 (16–23)	17 (14–20)	.87
Expiratory positive airway pressure initial, cm H_2O	4 (4–5)	5 (3.5–5)	.68
Expiratory positive airway pressure final, cm H_2O	5 (5–6)	5 (4–6)	.75
O_2 initial, L/min	2 (1–3)	2 (2–4.5)	.02
O_2 final, L/min	2 (1–3)	3 (2–4)	.03

Data are presented as median (IQR).

was 14 cm H_2O and was gradually increased to 17 cm H_2O, while median expiratory positive airway pressure remained stable at 5 cm H_2O. The process of pressure titration was performed over variable time (ie, hours to a few days) to facilitate tolerance. In 61 cases, supplemental oxygen was required through NIV at a median flow of 2 L/min (range 0–8 L/min) to target oxygen saturation depending on the baseline diagnosis at 88–92% for subjects with hypercapnia and > 94% for hypoxemic subjects. Pressure settings were similar between groups, but subjects with a shorter follow-up required higher oxygen flows (Table 3).

Commercially available full face masks were the interface of choice in 56 of 64 cases, with nasal mask or nasal pillows being preferred in 3 subjects. In 5 subjects, a rotational strategy was used in which subjects alternated between face masks and nasal pillows. Active humidification was added in 50 cases (78.1%) using either an external ($n = 28$, 43.7%) or an integrated ($n = 22$, 34.3%) humidifier. No differences in the choice of interface or use of humidification were noted between groups.

Follow-Up

Median duration of treatment with NIV was 58 (IQR 7–266) d over a follow-up period of 156 (IQR 26–531) d. No differences in duration of treatment were noted depending on the status on transplant waiting list at NIV initiation. A total of 18 subjects received a lung transplantation, with NIV being discontinued at time of transplant; 31 subjects died without transplant, and NIV was continued until the day of death in 17 cases.

Subjects with ≥ 6 months follow-up had a median duration of follow-up of 537 (IQR 302–728) d. In this group, duration of NIV treatment varied very significantly, ranging from 1 d to 1,145 d (median 268 [IQR 13–601] d).

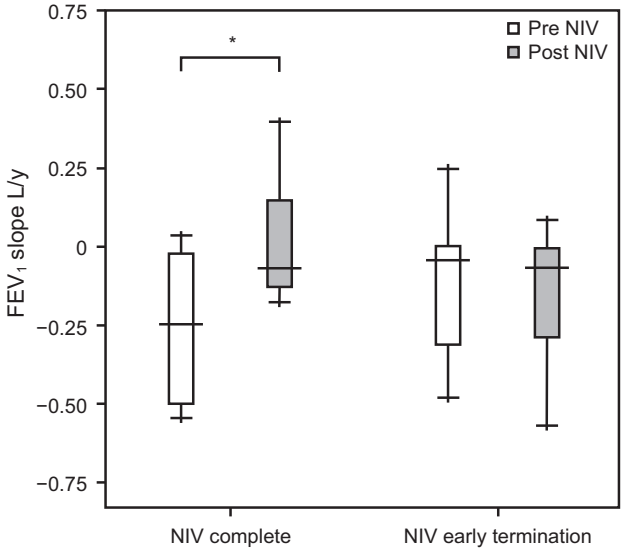

Fig. 2. FEV_1 depending on the use of NIV. Among subjects for whom NIV use with a follow-up > 6 months was available, subgroups were identified on the basis of the duration of NIV treatment during follow-up (ie, complete follow-up period or terminated early). * Indicates $P < .05$. NIV = noninvasive ventilation.

Thus, 2 subgroups were identified: 19 subjects continued using NIV for the whole duration of follow-up, whereas 12 subjects stopped using it within 6 months from start of treatment due to poor tolerance (early termination). The subgroups were similar for demographics and comorbidities. However, in the year preceding the start of NIV, best FEV_1 was lower (absolute value 0.87 [IQR 0.79–1.21] L vs 1.34 [IQR 1.07–1.49] L, $P = .048$; percent of predicted 28% [IQR 22–31] vs 38% [IQR 20.3–49.5], $P = .036$) and intravenous antibiotic requirements were higher (90 [IQR 50–154] d/y vs 55 [IQR 25–77] d/y, $P = .048$) among those who continued NIV throughout their follow-up. No differences in the modified Bhalla score or indications for starting NIV was observed across the subgroups. No differences in NIV settings, interface, or use of humidification were observed in the subgroups.

Within the first 12 months of starting treatment, FEV_1 decline did not change in those who stopped using NIV early (FEV_1 rate of decline prior to NIV –0.04 [IQR –0.35 to 0.03] L/y vs after NIV –0.07 [IQR –0.35 to 0.01] L/y, $P = .51$), but it improved in the subgroup of subjects who used NIV throughout the follow-up period (FEV_1 rate of decline prior to NIV –0.25 [IQR –0.52 to –0.02] L/y vs after NIV –0.07 [IQR –0.13 to 0.16] L/y, $P = .006$) (Fig. 2). No differences in the number of hospital days or intravenous antibiotic requirement before and after NIV were observed in either subgroup.

Subjects with < 6 months follow-up (33 of 64, 51.6%) had a median follow-up of 36 [IQR 16–102] d, and duration of NIV treatment was 24 [IQR 4.5–80] d. In this time frame, 24 (72.8%) subjects died, 8 (24.2%) received lung transplantation, and 1 (3%) relocated and transferred to another CF unit.

Complications

Ten subjects had complications with the use of NIV. In particular, pneumothorax requiring the insertion of chest drain while on NIV occurred in 4 cases (6.3%), one of whom had a known history of pneumothorax. Similarly, moderate to massive hemoptysis requiring temporary interruption of treatment was observed in 4 occurrences (6.3%), half of whom had a previous history of hemoptysis. No exacerbations of sinus disease or pressure ulcers were recorded. Failure of NIV was observed in 10 subjects. This led to cessation of treatment in 6 cases with no further escalation of treatment, whereas the remaining 4 underwent unsuccessful endotracheal intubation and invasive mechanical ventilation.

Discussion

Over the last 3 decades, NIV treatment has been routinely used in clinical practice to treat individuals with CF. While the use of NIV has been based on a sound pathophysiological rationale, clinical evidence to support its use so far has been scarce, especially with regard to outcomes of treatment.

In our center, approximately 10% of adults over a 10-years period received NIV on at least one occasion, with 60% of episodes occurring over the last 5 years. This frequency of use is in line with United Kingdom CF registry data collected between 2007 and 2015 (10.0%), but it is significantly higher than French surveys collected in 2008 (5.0%).[10,12]

There is presently insufficient data to define clear criteria for initiation of treatment because only a small number of randomized controlled trials of NIV in CF have been undertaken. In clinical practice, the rationale and indications for using NIV in CF often rely on evidence borrowed from other chronic respiratory diseases, such as COPD and chest wall restrictive disorders.

In our cohort, the indications for starting NIV were consistent with those previously reported in the literature.[10,11] The most common indications were chronic (48.5%) and acute (32.8%) hypercapnic respiratory failure associated with symptoms typical of carbon dioxide retention, such as early morning headaches and drowsiness. A significant minority of individuals were treated with NIV due to hypoxemia, in keeping with previous reports.[10,11] This use is in contrast with the latest guidelines from the American Thoracic Society and the European Thoracic Society on the use of NIV in the acute setting, which do not recommend NIV in hypoxemic patients other than as a trial in the ICU under close monitoring to avoid delaying intubation.[15]

Individuals with CF and advanced lung disease can be difficult to ventilate invasively due to severe air flow obstruction and high burden of secretions.[16] Endotracheal intubation and invasive mechanical ventilation are in fact historically associated with poor outcomes, adding justification to the use of noninvasive treatment instead. In this analysis, only a handful of subjects who experienced NIV failure underwent subsequent care in the ICU with invasive mechanical ventilation, and they all had a fatal outcome, in keeping with the literature.[17,18] As a result, severely hypoxemic patients with CF who do not improve with conventional oxygen treatment have limited options for escalation of respiratory support. Recent advances and experience in high-flow nasal cannula therapy in severe hypoxemia provides a potential alternative, but there is presently a lack of evidence to support its routine use in individuals with CF.[19-21]

The majority of individuals with CF receiving NIV were on the transplant waiting list or under consideration for lung transplantation. In the era of extracorporeal membrane oxygenation,[22] treatment with NIV remains a successful means to bridge CF patients to lung transplantation because its long-term use contributes to the stabilization of lung function.[23-27] Access to extracorporeal membrane oxygenation remains limited, and this technique is associated with risks and complications,[28,29] so NIV remains the mainstay in the symptomatic care of patients receiving end-of-life treatment.

Our data support the use of NIV as a bridge to lung transplantation, as 18 subjects successfully underwent transplant while receiving long-term NIV support. However, in our cohort NIV was started in most cases in subjects who had not yet been considered or had been declined transplant due to comorbidities. This highlights how the approach to the use of NIV has been changing over time. The follow-up period was relatively short because lost individuals had either received a lung transplant or died within 6 months of starting NIV. This raises the question as to whether an earlier intervention with NIV could have been more beneficial and might have improved survival for those awaiting lung transplantation. Larger cohort studies are needed, but with the recent introduction of cystic fibrosis transmembrane regulator modulator therapies, predicted outcome with NIV and natural history of disease may change significantly. Improving quality of life and symptom control remains an essential part of treatment, and in our cohort, NIV was also used as part of the end-of-life care to reduce the burden of symptoms, an indication recommended by Society of Critical Care Medicine.[30]

Individuals using NIV regularly over a period of $\geq$ 6 months showed significant benefit with stabilization of lung function. We witnessed a significant reduction in the yearly FEV_1 decline compared to that observed prior to NIV among those adherent to treatment long-term (Fig. 2). This was despite subjects having lower lung function and increased exacerbations prior to starting treatment.

Adherence to treatment is of the utmost importance in CF, and, due to the significant burden of treatment, poor adherence remains a significant problem, being as low as 40–50%.[31,32] This results in negative health outcomes, including progression of lung disease and rate of pulmonary exacerbations.[33] Due to the retrospective nature of the study, we are unable to provide daily hours of use for NIV; similarly, we cannot provide data relative to the adherence to the background CF treatment. Therefore, it cannot be ruled out that subjects who had a reduced rate of FEV_1 decline following NIV initiation were also more adherent to the remaining treatment. However, initiation of NIV did not affect intravenous antibiotic requirements or frequency of hospitalization, and the individuals who continued NIV treatment throughout follow-up had lower lung function and a more rapid decline in the 12 months prior to NIV, suggesting that the introduction of this treatment did in fact contribute to the stabilization of lung function.

The mechanisms underlying this effect are not completely clear. It is possible that NIV improves the performance of respiratory muscles during spontaneous breathing by unloading these muscles.[34] In addition, improvement of gas exchange, performance of respiratory muscles, and quality of sleep, which are results of using NIV,[35] can translate to improved exercise tolerance that in turn can lead to positive effects on lung function.

One advantage of using electronic patient record data is that we were able to include a large number of data fields as well as continuous data covering every episode of care for patients on NIV, in contrast to sporadic yearly measurements as recorded in the registries.[12] Data extraction from registries, however, has the benefit of including a larger population and more diverse clinical care. Our results are limited by the retrospective and single-center nature of the study. Despite all data being collected prospectively in real time, the data collection was driven by clinical need, resulting in a lack of systematic collection of blood gas analysis at specific time points and of data on quality of life.

The use of NIV in certain clinical scenarios including pneumothorax, hemoptysis, and severe sinus disease can be challenging, especially when options are limited. It was reassuring to find that the occurrence of these complications was low over the 10-y period and that a prior history of pneumothorax and hemoptysis resulted in low recurrence rate.

In our practice, NIV was set up by senior respiratory physiotherapists with the support of the sleep and NIV service as required. Treatment was started using several ventilator models, all of which were developed for home treatment. Modes of choice were pressure control or pressure support; none of the subjects in our cohort were treated with volume-targeted ventilation. Performing regular

reviews of the setting, including pressure and trigger sensitivity, and choosing a more physiological ventilation mode is of crucial importance to improve tolerance, comfort, and synchronization.

A similar individualized approach with regular assessment and review must be applied to the choice of interface, which is crucial to the success of NIV. This needs to take into account both patient and mask characteristics. In France, many centers report using a combination of custom-made and commercially available interfaces to optimize patients' tolerance of the treatment.[10] In our center, only commercially available interfaces are used. These are carefully selected to optimize comfort, balancing the needs and preferences of each patient with the availability of interfaces and costs. Full face masks are usually preferred in clinical practice for patients with acute respiratory failure who require short-term NIV and breathe with an open mouth due to high nasal resistance, whereas nasal masks, causing less claustrophobia and allowing for easier communication and oral intake, are deemed a better choice for long-term use.[36] In our cohort, however, oronasal masks were the interface of choice for most subjects, similarly to what has been reported in other groups of subjects with chronic respiratory failure.[37] Individuals with CF often experience nasal polyps, resulting in increased nasal resistance that would make nasal masks less suitable. In addition, people with CF are usually young and cooperative, and this facilitates their coordination with face mask removal to allow for airway clearance and expectoration as required. A rotational strategy was adopted in a handful of cases, mostly in subjects who required NIV for prolonged periods during the day as well. With this practice, no pressure ulcers were recorded. None of the subjects included in this analysis experienced significant mucus impaction, atelectasis, or exacerbation of sinus disease, most likely as a result of the use of active humidification in most cases (78.1%). Changes on chest computed tomography could not predict the likely benefit of NIV, as in our cohort, no correlation was observed between the modified Bhalla score and outcomes, tolerance, or complications.

Conclusions

NIV is used as adjunct therapy for the management of advanced CF lung disease in a manner similar to other chronic respiratory conditions. Subjects who continued treatment with NIV showed stabilization of lung function, despite the same frequency of exacerbations and intravenous antibiotics usage. Further large-scale studies are needed to define disease-specific criteria for initiation of NIV and appropriate machine settings, and to assess effectiveness of treatment. Critically, because this intervention is predominantly used by patients with end-stage lung disease, the impact on quality of life, symptom relief, and improvement in clinical outcome needs to be assessed.

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