The Current Practice of Noninvasive Ventilation in Patients With Cystic Fibrosis

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In patients with cystic fibrosis (CF), despite the availability of many different pharmacologic agents, lung function deteriorates and lung disease progresses and leads to hypercapnic respiratory failure in some patients. In such cases, noninvasive ventilation (NIV) seems to be a promising technique that can be used on demand. This review summarizes the current applications of NIV in clinical settings as well as findings of the clinical trials that involved the delivery of NIV on variable occasions, such as an adjunct to physiotherapy, in nocturnal hypoventilation, and acute and chronic respiratory failure. NIV has been used in patients with CF and with advanced lung disease who are not considered candidates for lung transplantation. It can stabilize lung function, although its effect on hypercapnia is not always evident. Nocturnal NIV has been used in patients with CF and with hypoventilation during sleep but without clear benefits on daytime P_{CO_2}. NIV as an adjunct to chest physiotherapy may be helpful when desaturation is observed during physiotherapy and when there are signs of respiratory muscle fatigue. NIV use in CF has been increasing, mainly in adult CF centers, and offers patients an opportunity to reach lung transplantation or to overcome acute hypercapnic respiratory failure. *Key words: noninvasive ventilation; cystic fibrosis; lung transplantation; physiotherapy; respiratory failure.*
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Introduction

Cystic fibrosis (CF) is a genetic disorder that affects many organ systems. However, it is the lower respiratory tract that accounts for the main disease burden. Despite the various available treatment modalities, lung function and lung disease will inevitably deteriorate, which results, in some patients, in respiratory failure. The underlying cause of CF manifestations is cystic fibrosis transmembrane conductance regulator protein dysfunction due to mutations of the gene that mediates its production, processing, and stability. Cystic fibrosis transmembrane conductance regulator protein dysfunction directly affects the chloride and bicarbonate transport, which, in turn, results in abnormal epithelial fluid transport in many organs.[1] The abnormal hydration of the airway surface leads to impairment of mucociliary clearance, which causes retention of thick mucus, failure of bacteria clearance, inflammation, and

respiratory infections. Bronchiectasis is a consequence of this cascade, and it can be evident in patients with CF even from infancy.[2,3] Lung function will inevitably deteriorate more rapidly, and some patients may end up in respiratory failure. Several factors, such as nutritional status, pancreatic status, chronic *Pseudomonas* infection, genotype, and, possibly, sex, have been related to severe lung disease progression.[4,5]

Respiratory failure is characterized by an increase in the respiratory load that cannot be counterbalanced efficiently by the central respiratory drive and respiratory muscle strength, and that leads to hypoventilation, hypercapnia, and hypoxemia.[6] Research results have shown the elastic load and the work of breathing increase as FEV_1 declines in subjects with CF.[7] When the FEV_1 decline is substantial, the patients who are affected adopt a shallow breathing pattern in an attempt to reduce the increased load. This strategy will maintain minute ventilation close to normal, but it will reduce alveolar ventilation, with a concomitant rise in P_{CO_2} and a drop in P_{aO_2}.[7] In such cases, the implementation of ventilatory support is justified, provided that all conventional therapies were tried without a satisfactory outcome.

Noninvasive ventilation (NIV) is the most promising technique of ventilatory support that allows avoiding tracheal intubation with its well-known complications and that can be used on demand, depending on the circumstances. The 2 main modes of delivery are volume and pressure control ventilation. Although there are specific guidelines for the initiation of NIV in diseases, for example, COPD and neuromuscular diseases, there are not, up to now, established criteria for the delivery of NIV in patients with CF. This review aimed to summarize the current applications of NIV in various clinical settings and the findings of clinical trials that involved the delivery of NIV in patients with CF.

Application of NIV in Patients With CF in Real-Life Clinical Settings

Data From Retrospective Studies

NIV was introduced as a bridge to transplantation, and Hodson et al[8] were the first who shared their clinical experience of 6 subjects who initiated NIV while awaiting heart-lung transplantation. The investigators' decision on the initiation of NIV was based on clinical and laboratory grounds due to the lack of established guidelines. The duration of NIV ranged from 3.5 to 36 days.[8] All but 1 subject survived until donor organs became available. Longer periods, up to 180 days, of nocturnal NIV, were subsequently described in 4 subjects.[9] Notably, 3 of the the subjects had initially been treated unsuccessfully with CPAP.[9] A reduction of P_{CO_2} and an increase of respiratory muscle strength were observed in all the subjects, along with an overall improvement and stabilization.[9] The small number of subjects in this case series did not allow a valid comparison between the before and after NIV measurements.

Next, a series of 10 cases was published.[10] The patients were started on NIV either while awaiting lung transplantation or after the initial assessment for lung transplantation. All had hypoxemia, hypercapnia, and low lung function (FEV_1 of ~15% predicted).[10] The duration of intervention ranged from 1 to 15 months; after 2 months, there was a significant increase of FEV_1 and FVC as well as stabilization of the blood gases, whereas, at 3 months, there was a significant improvement of hypercapnia and FVC.[10] The improvement in blood gases remained unchanged in 3 patients after 6 months of follow-up.[10] Also, there was a significant reduction in the duration of in-patient stay after 3 and 6 months of follow-up.[10] Three patients had lung transplantation, 4 died while on the waiting list, and 3 were still on NIV when this series was published.

With the advent of the 21st century, data from large CF centers or national registries with an adequate number of patients on NIV became available and an analysis of these data showed that the use of NIV was common in patients with advanced lung disease but who were not necessarily transplantation candidates. Madden et al[11] published a series of 113 subjects who were on NIV and O_2 (2-4 L/min) while waiting on a lung transplantation list or while on evaluation for lung transplantation, or with advanced lung disease but without being a candidate for transplantation. Overall, 28 of 113 subjects received a lung transplantation.[11] The duration on NIV ranged from 1 to 600 days, although it differed for each of the above-mentioned group of subjects. The investigators observed improvement of hypoxia but not a correction of hypercapnia.[11] The latter was attributed to the substantial dead space created by the abnormally dilated (bronchiectatic) bronchi.[11]

In contrast to the above-mentioned observations, Flight et al[12] in a retrospective study of 47 subjects found that the mean P_{aCO_2} improved significantly, from 50 mm Hg to 46 mm Hg, 1 year after NIV. However, the findings of these two studies[11,12] were not directly comparable because they used different types of ventilation modes. Flight et al[12] used pressure-controlled, pressure support, or target volume modes versus Madden et al,[11] who used a predetermined

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tidal volume in all the subjects. Furthermore, Flight et al[12] showed that the FEV_1 increased significantly the year that followed the start of NIV. The improvement in FEV_1 was associated with lower baseline FEV_1 values and a more rapid decline in FEV_1 the year that preceded the commencement of NIV.[12] Overall, 73% of the subjects responded to the application of NIV and were characterized as responders. It is of importance that the male subjects, the subjects with lower baseline FEV_1, or those with an accelerated rate of decline before NIV initiation were more likely to be responders to NIV delivery.[12]

Fauroux et al[13] used data from the French national CF registry and showed that, 1 year after its initiation, NIV had managed to reduce lung function deterioration. More specifically, they matched 41 subjects with advanced CF lung disease who had initiated NIV with a respective number of subjects who were not on ventilation.[13] They observed that 1 year after ventilation, the ventilated group had been stabilized with regard to the arterial oxygenation, FEV_1, and FVC values.[13]

Analysis of recent data from the United Kingdom CF registry demonstrated that, from 2007 to 2015, 10% of patients had at least 1 record of NIV use.[14] The annual incidence of NIV use among adults remained stable, whereas the prevalence increased over the 9 year observational period.[14] In the children, a small increase in the respective incidence and prevalence was observed.[14] The prevalence among the children was estimated at 1.7%, and the median ages for NIV initiation were 28.9 y and 13.5 y for the adults and children, respectively.[14] They also found that, after adjustment for age, sex, duration of intravenous treatment, and pancreatic insufficiency, FEV_1 increased significantly in adults but not in children.[14] After stratification for FEV_1, the adults with $FEV_1 < 40\%$ at the initiation of NIV showed a steeper increase of FEV_1.[14] Nevertheless, in terms of survival, NIV increased the odds for death or transplanstaion by 2 fold, this finding was propably related to the fact that patients with more severe disease are more likely to use NIV. In this cohort, only 26% of the patients with at least 1 record of NIV use had been evaluated for lung transplantation, which suggested that NIV was not simply used as a bridge to transplantation.[14]

In accordance with the previous findings, data from a single United Kingdom adult CF center indicated that 10% of the subjects were treated with NIV on at least 1 occasion.[15] Approximately half of them had been started on NIV because of chronic respiratory failure type II and one third because of acute respiratory failure. Among those who were on NIV for >6 months, the investigators noticed a significant reduction in the rate of FEV_1 decline, which indicated stabilization of lung function.[15] Such an improvement was not observed in the subjects who were on NIV for >6 months but terminated NIV prematurely because of poor tolerance.[15] Although NIV was administered to 18 of 56 subjects who eventually underwent successful lung transplantation, the majority initiated NIV without having been evaluated for transplantation.[15] Therefore, in agreement with the results from the United Kingdom CF registry, NIV was more than a bridge to transplantation.

It seems that, in everyday practice, NIV is used in patients with CF and advanced lung disease and hypercapnic respiratory failure, and not only when lung transplantation is imminent. NIV seems to stabilize lung function and delay its decline. The studies[10,11,12] inconsistent results in hypercapnia may be partly attributed to the small number of patients in some case series as well as the modes of ventilation support and the initial P_{aCO_2}. However, it is important to emphasize that NIV is of possible benefit in patients with hypercapnic respiratory failure.

Data From Surveys

In a nationwide survey from France that was undertaken in 2005, it was shown that 7.6% of the patients from the adult centers had used NIV, whereas only 1.2% of children ever needed NIV.[16] Most patients used NIV during an acute hypercapnic respiratory exacerbation or for persistent hypercapnia. Hypercapnia ($P_{aCO_2} > 48$ mm Hg up to 63 mm Hg, according to each center's clinical practice) was an indicator for NIV initiation, whereas $FEV_1 < 30\%$ was considered as a criterion only in 25% of the participating centers.[16]

A survey of pediatric CF centers from the United Kingdom and Australia demonstrated that 0.39% of the children needed NIV.[17] Only 31% of the centers reported that they followed a specific protocol for NIV institution, without clarifying whether the protocol was specific for CF. There was no agreement among the centers for the definition of hypoxia and hypercapnia. Nevertheless, it seems that, among pediatric patients, the need for NIV is limited, possibly due to relatively good lung function and the low prevalence of respiratory failure.

It is evident that there is a trend of increasing use of NIV, at least among adults, mainly for hypercapnic respiratory failure, either acute or chronic. It should be noted that $P_{aCO_2} > 50$ mm Hg, among other variables, is a predictor of mortality in CF.[18] However, there are no validated criteria for values of P_{aCO_2} above which NIV should be implemented. Data extrapolating from other diseases, for example, COPD, may not be relevant for CF due to different pathophysiologic mechanisms of the disease. Furthermore, even if NIV was initially introduced for patients awaiting lung transplantation, there is no consensus that all patients on waiting lists for lung transplantation should be put on NIV because there are no data that support better outcomes.

Clinical Trials of NIV Application in Subjects With CF in Variable Situations

Daytime While at Rest

In 1998, a small study of subjects with CF was performed that evaluated the immediate impact of NIV on blood gases in these subjects while they were awake.[19] Eight subjects with chronic respiratory failure were evaluated before and after the application of nasal bi-level NIV for 20 min.[19] The results showed a significant increase in S_{pO_2}, a significant but modest decrease of transcutaneous P_{CO_2} and breathing frequency.[19] Tidal volume increased and minute ventilation decreased but both in a nonsignificant manner.[19] The investigators attributed their results to better alveolar ventilation and/or to decreased oxygen consumption by the respiratory muscles.

Twenty years later, Sklar et al[20] compared the physiologic effect of NIV application to that of high-flow nasal cannula (HFNC) in subjects with CF who had been previously stabilized with the use of ventilatory support. The enrolled subjects received HFNC and NIV for 30 min in a random crossover order. It was found that HFNC was superior to NIV with regard to the reduction in breathing frequency and minute ventilation, but there was no difference in diaphragmatic activity per breath.[20] The investigators advocated the superiority of HFNC to NIV, acknowledging as a limitation of their study that all the subjects were enrolled after having been stabilized by ventilatory support.[20]

Daytime During Exercise

Short-term benefits on exercise were also found in an open randomized crossover clinical trial in children and adolescents with moderate impairment of lung function (FEV_1, 40%-80% predicted).[21] The subjects performed a 6-min treadmill walking test with and without NIV, with an interval of 24–48 h between the tests. The walking distance was significantly longer while on the NIV. FEV_1, tidal volume, and minute ventilation were also measured after the end of the test and found to have been improved significantly with NIV. In contrast, without NIV, oxygen saturation dropped and breathing frequency increased 5 min after the treadmill walking test. The results indicated that NIV in cases of cardiorespiratory overload, for example, with exercise, optimizes ventilation and increases the capacity of subjects to participate in physical activity.[21] It is of note, however, that the FEV_1 of all the participating subjects was at least 40% predicted.[21] Therefore, conclusions cannot be extrapolated for subjects with severe lung disease and $FEV_1 < 40\%$ predicted.

Daytime During Chest Physiotherapy

Several clinical trials evaluated the contribution of NIV as an adjunct in airway physiotherapy for subjects with CF. The initial hypothesis was that the increase of tidal volume through positive pressure would improve sputum expectoration while reducing, at the same time, the work of breathing. Fauroux et al[22] evaluated, for the first time, the impact of inspiratory pressure-support ventilation on respiratory muscle fatigue in children and adolescents with CF during airway clearance therapy with the use of the forced expiratory technique. They observed that respiratory muscles functioned better during the sessions of airway clearance therapy with NIV.[22] A reduction of desaturations during physiotherapy was also noticed.[22]

Four years later, Holland et al[23] assessed the impact of NIV administered by a bi-level device in adults with moderate-to-severe CF lung disease during an exacerbation. They also noticed that inspiratory muscle strength was preserved and the respective expiratory strength was increased during the sessions of airway clearance therapy with accompany NIV.[23] Fewer desaturations were also recorded, most likely due to better alveolar ventilation during NIV.[23] There was no difference with regard to the weight of collected sputum with or without the application of NIV during physiotherapy. The amount of sputum also did not differ in another study conducted in adolescents and adults with severe CF and exacerbations, in which the investigators compared standard chest physiotherapy with combinations of positive expiratory pressure, CPAP, and NIV.[24] Likewise, Stanford et al[25] did not find a difference in the wet weight of 24-h sputum in a randomized crossover trial of NIV-supported physiotherapy or physiotherapy alone. The study was performed during the last 2 days of the subjects' hospitalization due to pulmonary exacerbation. The investigators observed, however, that the mean oxygen saturation was 2% higher during NIV treatment, although the clinical importance of this difference is doubtful.[25] No spirometric differences were noticed between the 2 treatment regimens (NIV supported physiotherapy or physiotherapy alone).

Dwyer et al[26] evaluated the effect of NIV as an adjunct to an airway clearance regimen in a group of 40 adults with CF. This study was also performed during hospitalization for an exacerbation. It was noticed that the FEV_1 at discharge was significantly higher for the group that used NIV as an adjunct to airway physiotherapy.[26] They also found that the group on NIV reported significantly lower fatigue levels on the Schwartz fatigue scale at discharge than the control group.[26]

Stanford et al[27] evaluated the effect of NIV as an adjunct to home airway clearance techniques. In this small study, adult subjects with CF were asked to record, on visual analog scales, the ease of clearance and the breathlessness with chest

physiotherapy before and after addition of NIV to their normal physiotherapy routine.[27] All the subjects used NIV for >1 year. There was a significant difference for both parameters, with easier sputum clearance and reduced breathlessness after the use of NIV.[27] The observed subjective ease of sputum clearance after NIV use seemingly contradicts previous study results,[23,24,25] which did not show a difference in expectorated sputum weight. However, these studies are not comparable because Stanford et al[27] assessed the long-term effect of NIV as an adjunct to airway clearance techniques and not the short-term effect of NIV, as the previous studies[23,24,25] did.

In a 3-month randomized trial by Rodriguez Hortal et al[28] NIV physiotherapy was compared with the standard positive expiratory pressure method. No statistically significant difference was found between baseline spirometry values and those after each of the physiotherapy regimens; however, the investigators found a significant reduction in lung clearance index after NIV compared with positive expiratory pressure, although it was not clear if this was clinically meaningful.[28] It seems that NIV as an adjunct to chest physiotherapy may be helpful when significant desaturation is observed during physiotherapy and when there are signs of respiratory muscle fatigue. In general, however, the existing data are not sound enough, mainly because of the small sample size of studies, and a definite conclusion is not warranted.

Nighttime During Sleep

Another situation in which hypoxia can occur in patients with CF is sleep. The majority of studies showed that FEV_1 correlates directly with nocturnal hypoxia,[29] which implies that patients with severe lung disease may need supplemental oxygen during sleep. Gozal[30] evaluated 6 subjects with $FEV_1 < 40\%$ predicted in room air during night sleep. These subjects were then re-evaluated on 2 different nights, one night while on low flow oxygen therapy and the other night while on bi-level NIV. The mean oxygen saturation significantly increased with either treatment modality, and there was no significant difference between NIV and oxygen therapy; however, transcutaneous P_{CO_2} decreased significantly with NIV and increased significantly with supplemental oxygen compared with baseline.[30] There was no adverse effect of NIV on sleep architecture or the arousal index.[30] These findings were corroborated in a similar study,[31] which included 13 adults in whom it was observed that the implementation of NIV significantly reduced the rise of transcutaneous P_{CO_2} seen during the transition from non-REM to REM sleep. Furthermore, the tidal volume remained stable during the transition from non-REM to REM sleep when the subjects were on NIV, whereas it tended to fall while on room air or supplemental oxygen, which indicated that hypoventilation occurred while on supplemental oxygen but was attenuated while on NIV.

In another study, by Young et al,[32] which lasted 6 weeks for each arm (room air, oxygen, bi-level NIV) and included 8 subjects with impaired nocturnal gas exchange and daytime hypercapnia, the 3 modes of intervention did not affect daytime blood gases. None of the 3 interventions had any effect on lung function, but NIV increased exercise performance significantly, which augmented the shuttle distance on the modified shuttle test.[32]

A more recent long-term study, of 12 months' duration, compared 2 groups of subjects with CF with sleep desaturation who were randomly allocated to either NIV or supplemental oxygen during sleep.[33] The primary outcome measure was event-free survival, in which events were defined as worsening hypercapnia, lung transplantation, or death. The NIV group had 33% and 46% more event-free survival at 3 and 12 months compared with the supplemental oxygen group.[33] No significant differences were observed between the groups in spirometry, blood gases, sleep quality, or hospitalizations.

By using data from some of the aforementioned trials, Moran et al[34] performed a meta-analysis, which provided support on the use of NIV with oxygen because this intervention may improve gas exchange during sleep in the subjects with moderate-to-severe CF disease. Up to now all the studies on the application of nocturnal NIV in patients with hypoventilation during sleep support its use. Nevertheless, these studies were not able to show significant benefits on daytime levels of P_{aCO_2}, although this may be related, to some extent, to the limited number of participants and the varying baseline daytime values of P_{aCO_2}.

Implications for Practice: Limitations of NIV

Because specific guidelines are not available, the application of NIV should be individualized based on the patient's situation, the response to the initial NIV sessions, and the relevant CF center experience. In accordance with the proposal by Fauroux[35] and based on the aforementioned clinical studies, we suggest that NIV should be considered in patients with daytime hypercapnia, acute hypercapnic respiratory failure not responding to conventional treatments, and desaturation or substantial fatigue with airway clearance therapy. It could also be considered in nocturnal hypoventilation documented by an overnight sleep study.

However, it should be kept in mind that there are some limitations with the application of NIV even in patients with CF who may theoretically benefit from NIV initiation. Specifically, it is difficult to apply NIV in patients who are not cooperative or feel discomfort, in those with upper airway pathology, and in patients who retain excessive secretions.[16] Furthermore, patients with established NIV may have to discontinue it either because of discomfort from

abdominal distention[16] or skin breakdown in the face area of the mask,[36] or from rarely seen complications such as pneumothorax and hemoptysis.[15]

Summary

NIV is a therapeutic mode for patients with CF and with advanced lung disease who have hypercapnic respiratory failure, either acute or chronic, that cannot be managed by conventional therapies. However, there is no consensus on the timing of NIV initiation in different circumstances such as exacerbation, nocturnal hypoventilation, chronic respiratory failure, airway clearance therapy, and exercise. Even for people on waiting lists for lung transplantation, it is not clear that they should be managed with NIV before transplantation. There is a need for long-term clinical trials; however, these are difficult due to ethical issues. Nevertheless, the use of NIV mainly increases in adult CF centers because it is used as an adjuvant therapeutic tool that helps patients to reach the ultimate goal of lung transplantation or to overcome a situation of hypercapnic respiratory failure.

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