

# Practice of Noninvasive Ventilation for Cystic Fibrosis: A Nationwide Survey in France

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**BACKGROUND:** No guidelines are available for noninvasive ventilation (NIV) for cystic fibrosis (CF). **OBJECTIVE:** To survey and evaluate the use of NIV for CF in France. **METHODS:** We surveyed the coordinator physicians of every accredited CF center in France. **RESULTS:** The respondents represented 36 centers (15 pediatric centers, 13 adult centers, and 8 centers that see both pediatric and adult patients), which had a total of 4,416 patients with CF at the time of the study, 168 (3.8%) of whom were using NIV. NIV was being used more often in the adults centers (7.6% of these patients) than in the pediatric centers (1.2% of these patients) or adult-and-pediatric centers (4.1% of these patients) ( $P = .01$ ). All the respondent centers use NIV as first-line treatment for severe hypercapnic respiratory exacerbation and for stable diurnal hypercapnia, especially when associated with sleep disturbance. Bi-level pressure-targeted ventilation is the preferred ventilation mode. Settings are adjusted based on arterial blood gas values, noninvasive evaluation of patient-ventilator synchrony, patient comfort, and sometimes a sleep study. The surveyed centers reported a number of expected benefits from NIV, but few of those benefits have been proven. Problems with NIV are common and limit its use. **CONCLUSIONS:** We found a relative homogeneity in these French centers' stated indications for and use of NIV, which highlights their numerous expectations about the benefits of NIV, which contrasts with the few validated benefits. **Studies of the benefits of NIV are needed.** *Key words:* noninvasive ventilation, cystic fibrosis, CF, respiratory failure, hypercapnia, home care, prescription, guidelines. [Respir Care 2008;53(11):1482–1489. © 2008 Daedalus Enterprises]

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Table 1. Cystic Fibrosis Centers and Number of Patients On NIV

	Total	Type of Center			<i>P</i>
		Pediatric Only ( <i>n</i> = 15)	Pediatric and Adult ( <i>n</i> = 8)	Adult Only ( <i>n</i> = 13)	
Patients ( <i>n</i> )	4,416	2,078	975	1,363	.01
Patients per center (mean ± SD)	123 ± 75	139 ± 84	122 ± 63	105 ± 66	.78
Patients on NIV ( <i>n</i> and % of total)	168 (3.8)	24 (1.2)	40 (4.1)	104 (7.6)	.01
Patients on NIV per center (mean ± SD)	4.5 ± 6.9	1.6 ± 2.8	5.0 ± 10.1	7.4 ± 7.0	.006
Patients who started NIV in the past year ( <i>n</i> and % of patients on NIV)	79 (47)	14 (58)	8 (20)	57 (55)	.003

NIV = noninvasive ventilation

## Introduction

Cystic fibrosis (CF) is a common genetic disease in the white population. Most of the morbidity and mortality from CF is due to the involvement of the lungs, which is progressive airflow obstruction from mucus plugging, bronchial inflammation, and parenchyma destruction secondary to bronchiectasis. CF is characterized by progressive and ineluctable decline in lung function, which progresses to end-stage respiratory failure.<sup>1</sup>

Although noninvasive ventilation (NIV) is less commonly used in CF than in other chronic lung diseases, such as chronic obstructive pulmonary disease (COPD), there is a definite physiologic rationale for NIV in advanced CF. Short-term physiologic studies with awake and asleep subjects found that NIV reduces respiratory muscle load and work of breathing,<sup>2-4</sup> and increases minute ventilation,<sup>2-5</sup> and thus improves alveolar ventilation and gas exchange.<sup>2-6</sup> But, despite those encouraging results, few patients are treated with NIV, which is often proposed only to patients with very advanced lung disease. Possible explanations include the lack of clearly validated criteria for NIV, controversy about ventilation modes and settings, skepticism about long-term efficacy, and poor acceptance by patients, who already spend considerable time on treatment.

In France the care of patients with CF is organized in accredited pediatric, adult, or adult-and-pediatric CF care centers nationwide. This national network is united by the National Cystic Fibrosis Federation, whose goals are to improve and harmonize patient care, evaluate practices, and implement clinical trials. This network gives an opportunity to evaluate the practice of NIV in patients with CF in France. We surveyed the CF centers on their NIV practice and compared the responses from the pediatric, adult, pediatric-and-adult centers.

## Methods

The National Cystic Fibrosis Federation includes several groups that are specialized in one aspect of the mul-

ti-organ dysfunction of CF (Appendix). Our group, the Chronic Respiratory Insufficiency Group, comprises pediatricians, pulmonary pediatricians, adult pulmonologists, and respiratory physiotherapists interested in the different aspects of severe CF lung disease. Our major priority was to evaluate NIV use and develop national guidelines. We designed a survey on various aspects of NIV for CF, including indications, initiation, ventilation modes, settings, choice of equipment, follow-up, expected benefits, problems with NIV, and the number of patients receiving short-term versus long-term NIV. We used the American Academy of Sleep Medicine definition of sleep-disordered breathing.<sup>7</sup> The final form of the survey was approved by all members of the Chronic Respiratory Insufficiency Group, and the survey was sent to the coordinator CF physician of each accredited CF center, during the first 3 months of 2005. The centers that did not reply by the end of June 2005 were contacted and we sent them the survey again.

This study did not require approval of the institutional review board.

Differences between the pediatric, adult, and adult-and-pediatric centers were evaluated with the chi-square test for categorical variables and the Kruskal-Wallis rank sum test for continuous variables (StatView, SAS Institute, Cary, North Carolina). Values are reported as percentages or as median and interquartile range. *P* values < .05 were considered significant.

## Results

### Cystic Fibrosis Centers and Patients On NIV

Fifteen pediatric centers, 13 adult centers, and 8 adult-and-pediatric centers responded to the survey (Table 1). The centers had 4,416 patients with CF. Only 3 centers failed to respond to the first mailing. Eleven centers (5 pediatric centers and 6 adult-and-pediatric centers) did not participate in the study. All those centers were small (< 50 patients per center) and declined to participate because they had no experience with NIV, no pulmonologist or

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Table 2. Reported Indications for NIV for Patients With Cystic Fibrosis in 36 Participating Centers

Indication*	Pediatric Centers (n = 15)	Pediatric and Adult Centers (n = 8)	Adult Centers (n = 13)	P
Exacerbation				
During an exacerbation (%)	87	88	100	.30
After an exacerbation (%)	47	63	31	.07
According to a given P <sub>aCO<sub>2</sub></sub> value (%)	87	63	100	.18
if P <sub>aCO<sub>2</sub></sub> more than this value†	45 (45–55 mm Hg)	45 (45–50 mm Hg)	45 (45–50 mm Hg)	.90
Lung function				
Diurnal hypercapnia (%)	93	88	92	.82
if P <sub>aCO<sub>2</sub></sub> more than this value†	63 (61–64 mm Hg)	50 (45–58 mm Hg)	48 (45–50 mm Hg)	.78
According to a given FEV <sub>1</sub> % predicted value	40	25	15	.72
if FEV <sub>1</sub> % predicted less than this value†	35 (32–35%)	25 (22–28%)	30 (25–35%)	.36
Sleep disturbance				
Clinical symptoms (%)	53	38	38	.69
Nocturnal desaturation (%)	67	25	23	.03
Nocturnal hypercapnia (%)	53	50	15	.08
Abnormal polysomnography (%)	33	38	15	.44
Insufficiency of LTOT (%)	27	25	62	.20
Weight loss (%)	27	0	23	.37
Lung transplantation				
Lung transplantation being considered (%)	67	63	54	.09
Patient on lung-transplant list (%)	60	63	69	.69

\* Multiple answers were possible for each indication.  
† Median and interquartile range.  
FEV<sub>1</sub> = forced expiratory volume in the first second.  
LTOT = long-term oxygen therapy.

physiotherapist involved in NIV, had not used NIV in the past 2 years, or (only at the pediatric centers) the patients were doing well and had good lung function. The total number of patients (4,416) in the 36 centers that participated in the study was nearly the total number of patients in the French national CF “Observatory” (census) in 2004 (4,533 patients).

Whereas the mean total number of patients per center was not statistically different between the 3 types of centers, the number of patients using NIV was significantly greater in the adult CF centers (104 of 1,363 patients, 7.6%) than in the pediatric centers (24 of 2,078 patients, 1.2%) or the adult-and-pediatric centers (40 of 975 patients, 4.1%) ( $P = .01$ ). A high proportion of patients (20%–58%) had started NIV in the 12 months before the survey.

### Indications for NIV

Table 2 lists the reported indications for NIV. Nearly all the centers use NIV for severe hypercapnic respiratory exacerbation, but they do not systematically continue NIV after exacerbation. NIV is considered for persistent hypercapnia. Between the 3 types of centers there was close agreement about the P<sub>aCO<sub>2</sub></sub> value that indicates NIV (approximately 45 mm Hg).

A very high percentage (88–93%) of the centers use stable diurnal hypercapnia as a criterion to propose NIV.

The cut-off P<sub>aCO<sub>2</sub></sub> range used by the 3 types of centers was 48–63 mm Hg. Forced expiratory volume in the first second (FEV<sub>1</sub>), taken independently of other criteria, was considered less pertinent than P<sub>aCO<sub>2</sub></sub> in the prescription of NIV. An FEV<sub>1</sub> < 25–30% of predicted was considered an NIV criterion by only 25% of the adult-and-pediatric centers and 15% of the adult centers.

Clinical symptoms of sleep disturbance and nocturnal desaturation were more important to the pediatric centers than the adult centers in the prescription of NIV. Half of the pediatric and adult-and-pediatric centers, but only 15% of the adult centers, considered nocturnal hypercapnia an important factor. A minority of centers take sleep studies into account. Inefficacy of long-term oxygen therapy (LTOT) (eg, persistent hypoxemia despite LTOT) was an important criterion among the adult centers. For one quarter of the pediatric and adult centers, weight loss or insufficient weight gain were an NIV criterion.

NIV was not systematically proposed to patients on the lung-transplant list, even at the adult centers accredited for lung transplantation.

### Initiation of NIV

In all 3 types of centers, several specialists may be involved in the initiation of NIV, as reflected by the multiple responses (Table 3). NIV is generally initiated by the

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Table 3. Initiation of NIV in Patients With CF in 36 Participating Centers

	Pediatric Centers (n = 15)	Pediatric and Adult Centers (n = 8)	Adult Centers (n = 13)	P
<b>Clinician Who Initiated NIV*</b>				
CF specialist (%)	87	75	77	.59
Non-CF intensive care specialist (%)	27	25	45	.66
Non-CF pulmonologist (%)	7	25	23	.46
Respiratory physiotherapist (%)	13	13	54	.04
<b>Who Chose the NIV Equipment*</b>				
Medical team (%)	100	100	100	.06
Physiotherapist team (%)	13	0	48	.04
Home-care organization (%)	27	13	0	.11
<b>Ventilation mode†</b>				
Pressure-controlled (%)	53	63	92	.18
Volume-controlled (%)	53	38	69	.60
With PEEP (%)	60	63	77	.90
PEEP (median and interquartile range cm H <sub>2</sub> O)	4.0 (3.0–5.0)	4.0 (3.7–4.3)	4.0 (4.0–5.0)	.90
<b>Humidification</b>				
Systematically proposed (%)	13	37	15	.48
Only if nasal discomfort (%)	54	50	85	.12
Never proposed (%)	33	13	0	.04
<b>Interface</b>				
Exclusively commercially available masks (%)	60	75	77	.90
Exclusively custom-made masks (%)	0	0	0	.99
Commercially available or custom-made masks (%)	40	25	23	.83
Exclusively nasal masks (%)	67	25	8	.02
Exclusively face masks (%)	0	0	0	.99
Nasal or face masks (%)	33	75	92	.02

\* Possibility of multiple answers  
† Several modes may have been used in some patients.  
NIV = noninvasive ventilation  
CF = cystic fibrosis  
PEEP = positive end-expiratory pressure

CF team specialist, or less commonly by a non-CF physician such as an intensive care specialist or a non-CF adult pulmonologist. Respiratory physiotherapists participated in NIV initiation more often in the adult centers than in the pediatric or adult-and-pediatric centers.

The type of ventilator and interface was always chosen by the medical team, with the assistance of the respiratory physiotherapists at the adult centers, and by the technicians of the home-care centers at a quarter of the pediatric centers.

Pressure-controlled and volume-controlled modes are used equally in the pediatric centers, whereas the adult centers prefer pressure-controlled modes. More than half of the centers add positive end-expiratory pressure.

Humidification is generally proposed only if the patient has nasal discomfort, and mostly at the adult centers. Humidification is never proposed in one third of the pediatric centers.

Commercially available masks are preferred by all 3 types of centers, but some centers also use custom-made

masks. Face masks are used significantly more often with adult patients than with pediatric patients.

### NIV Settings, Adherence, and Follow-up

Approximately two thirds of the centers use overnight pulse oximetry to adjust the ventilator settings. Transcutaneous or exhaled CO<sub>2</sub> measurement is uncommon (Table 4). The majority of centers set the ventilator based on arterial blood gas values during NIV, rather than during spontaneous breathing. Patient-ventilator synchrony, assessed via clinical observation and patient comfort, is an important criterion for all 3 types of centers. Half of the centers also base ventilator settings on sleep studies.

The pediatric and adult-and-pediatric centers prefer overnight hospitalization for follow-up of patients on NIV, associated with routine out-patient visits. In about a quarter of the adult centers the follow-up of a patient on NIV does not differ from that of a patient not on NIV.

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Table 4. Criteria for NIV Settings and Follow-up in 36 Participating Centers

	Pediatric Centers ( <i>n</i> = 15) %	Pediatric and Adult Centers ( <i>n</i> = 8) %	Adult Centers ( <i>n</i> = 13) %	<i>P</i>
NIV settings based on*				
Pulse oximetry	67	75	69	.95
Transcutaneous or exhaled P <sub>CO<sub>2</sub></sub>	13	0	0	.34
ABG during NIV	80	88	100	.82
ABG during spontaneous breathing	60	50	77	.57
Minute ventilation during NIV	50	25	69	.29
Patient-ventilator synchrony	80	75	77	.89
Patient comfort during NIV	73	88	92	.65
Sleep study with NIV	53	50	54	.98
Follow-up via*				
Overnight hospitalizations	60	62	54	.83
Out-patient visits	40	25	62	.33
Follow-up identical for patients on and not on NIV	0	13	23	.14

\* Multiple answers possible.  
NIV = noninvasive ventilation  
ABG = arterial blood gas values

### Expected Benefits of and Problems With NIV

The centers' expectations about NIV benefits are very high and comparable between the 3 types of centers (Table 5). A high percentage of the centers expect a decrease in general fatigue and an increase in P<sub>aO<sub>2</sub></sub>, followed by an improvement in exercise and physiotherapy tolerance, a decrease in P<sub>aCO<sub>2</sub></sub>, a reduction in the rate and severity of respiratory exacerbations, and a stabilization of the decline of lung function. Weight gain is expected as a minor benefit. Some centers also expect improved quality of sleep (2 centers), quality of life (3 centers), or survival (1 centers).

Adverse effects and problems associated with NIV are common and reported by all the centers (see Table 5). The most frequent problems are difficulty sleeping with the ventilator, and intolerance of the interface. Nearly three quarters of the patients found NIV too constraining. This may explain patient preference for LTOT.

Absence of a clear subjective benefit for the patient is another important cause of NIV failure. Abdominal distention and patient refusal were nonsignificantly more common in the adult patients. One center reported that patients stopped using NIV because of excessive secretions. Two centers reported that patients stopped using NIV because it disrupted family life.

The physician-estimated patient adherence to NIV was very high and similar in all 3 types of centers (72–83%). Most of the centers also rely on patients' report of adherence and on the recording of the ventilator use, which is regularly checked by the home-care organization.

### Discussion

This study of French CF centers is the first to give an extensive overview on the prescription, initiation, follow-up, expected benefits, and problems of NIV in pediatric and adult patients with CF. In France the management of CF patients seems to be very homogeneous among the pediatric, adult-and-pediatric, and adult centers, despite the greater experience with NIV at the adult CF centers. The primary indication for NIV is stable diurnal hypercapnia, though certain other factors, such as respiratory exacerbation or sleep disturbance, are also important. The survey responses indicate that the centers have high expectations about the potential benefits of NIV, but this contrasts with the lack of evidence of those benefits in this CF population.

Although this survey reflects the NIV prescription habits for patients with CF in France, the data are strengthened by the high survey-response rate and the fact that the number of patients treated by the 36 centers that responded was comparable to the number of patients in the French CF Observatory in 2004. As expected, significantly more patients are treated with NIV in the adult centers than in the pediatric or pediatric-and-adult centers, because of the progressive lung-function decline in CF.

Respiratory exacerbation was the most common criterion to initiate NIV. In adults admitted to the intensive care unit for severe CF respiratory exacerbation, NIV has had good results, including survival or successful lung transplantation in more than half the patients.<sup>8-10</sup> A retrospective multicenter study of 60 hospitalizations of 42 adult patients with CF admitted between 2000 and 2003 in 6

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Table 5. Expected Benefits of, Observed Problems With, and Adherence to NIV in 36 Participating Centers

	Pediatric Centers (n = 15) %	Pediatric and Adult Centers (n = 8) %	Adult Centers (n = 13) %	P
Expected improvement in*				
General fatigue	80	100	100	.22
Physiotherapy tolerance	67	75	92	.55
Exercise tolerance	53	50	54	.99
Exacerbation rate	33	13	54	.23
Exacerbation severity	53	50	46	.91
P <sub>aO<sub>2</sub></sub>	40	75	62	.30
P <sub>aCO<sub>2</sub></sub>	80	100	100	.99
Stabilized lung function	67	13	46	.29
Weight gain	60	38	46	.53
Other†	0	10	20	.21
Problems observed*				
Difficulty sleeping with NIV	60	88	85	.40
Preference for oxygen therapy	13	25	15	.73
No subjective benefit	60	50	38	.44
Too constraining	47	75	77	.37
Problems with the interface	73	63	54	.64
Refusal	27	13	54	.88
Abdominal distension	17	0	54	.04
Other‡	0	0	34	.21
Adherence to NIV assessed via				
Patient's report	53	75	77	.57
Home-care organization report	53	63	77	.76

\* Multiple answers possible.

† Other: improved quality of sleep (2 centers), improved quality of life (3 centers), longer survival (1 center)

‡ Other: disruption of family life (2 centers), excessive secretions (1 center)

NIV = noninvasive ventilation

intensive care units in and around Paris confirmed the efficacy of NIV. NIV was used in 57% of cases and was successful in 67% of those patients.<sup>11</sup>

Stable persistent diurnal hypercapnia was the second most frequent indication for NIV. Interestingly, there seems to be little difference in the thresholds for starting NIV in the acute versus the chronic setting. The P<sub>aCO<sub>2</sub></sub> value above which the respondent centers propose NIV for patients with CF is lower than that recommended for patients with COPD.<sup>12</sup> Long-term NIV for COPD seems to be more effective in patients who have greater hypercapnia. Uncontrolled studies found that patients with P<sub>aCO<sub>2</sub></sub> that reached 60 mm Hg had a greater P<sub>aCO<sub>2</sub></sub> decrease and a greater improvement in quality of life than did patients with less severe hypercapnia.<sup>13,14</sup> That NIV is prescribed for CF patients who have moderate hypercapnia may be explained by the pathophysiology of respiratory failure in CF. Even with moderate hypercapnia, patients with CF have to cope with a very high work of breathing. Young patients with CF and mean FEV<sub>1</sub> of 30% of predicted have esophageal and diaphragmatic pressure-time products that are 3–5-fold the normal values.<sup>15</sup> NIV efficiently unloads the respiratory muscles in CF patients

with a comparable level of lung function.<sup>2,4</sup> In the present study, in the adult centers LTOT inefficacy (persistent hypoxemia despite LTOT) was a strong indication for NIV.

NIV is adjusted on the classical criteria such as overnight pulse oximetry, arterial blood gas values during and between periods of NIV, and recording of minute ventilation on the ventilator when possible. Surprisingly, transcutaneous or exhaled CO<sub>2</sub> is rarely measured, though nocturnal hypercapnia is an indication for NIV. Sleep studies with NIV are performed by only half of the centers. In the present study, the importance accorded to the patient-ventilator synchrony is also surprising. Evaluating patient-ventilator synchrony is difficult if electromyography (with surface electrodes or esophageal probe) or esophageal manometry is not possible. In the majority of centers, patient-ventilator synchrony is therefore evaluated based on noninvasive measurements and assessments. All the centers are aware of the importance of patient comfort, which correlates with unloading of the respiratory muscles and, thus, the efficacy of NIV, in patients with CF.<sup>2</sup>

Concerning follow-up of patients on NIV, no clear evaluations or recommendations have been made. Because of the importance of checking the improvement of nocturnal hypoventilation, the pediatric and adult-and-pediatric centers prefer a follow-up with overnight hospitalization, which seems to be more difficult to set up with adult patients, because they are more reluctant about hospitalization. However, in France home care for patients with chronic respiratory insufficiency is very well organized, by nonprofit and private networks.<sup>16-18</sup>

The long list of expected NIV benefits contrasts with the limited number of evidence-supported benefits. Several short-term physiologic studies found that NIV improves gas exchange, both awake<sup>2-4</sup> and asleep.<sup>5,6,19</sup> But only 2 short-term studies have found that noninvasive pressure support is associated with fewer desaturations and improved respiratory-muscle performance during physiotherapy.<sup>20,21</sup> NIV may also improve exercise tolerance.<sup>22,23</sup> Even if there is a general consensus for NIV during CF exacerbation, the superiority of NIV to standard treatment has not been established by randomized controlled trials. Also, the effect of NIV on exacerbation rate and severity has not been established. Recent data from the French national CF Observatory were the first to indicate that NIV is associated with stabilization of lung-function decline in patients with severe CF lung disease.<sup>24</sup> NIV decreases respiratory load and energy consumption from breathing, so it seems reasonable to expect a weight increase, but no such benefit was observed in the French national CF Observatory study.<sup>24</sup>

In the pediatric centers the most common NIV problems were intolerance of the interface, difficulty sleeping with NIV, and absence of subjective benefit. In the adult and adult-and-pediatric centers, NIV was considered too constraining, probably because of the heavy burden of the other daily treatments, such as aerosols, which are very time-consuming. Psychological reasons for NIV failure, such as NIV refusal, were reported by half of the adult centers. Psychological refusal may be more important for NIV than for other therapies, because the ventilator and its related equipment are time-consuming, cumbersome, and may be considered an obvious escalation of treatment that reflects the progression of disease severity.

### Limitations

Because of our study design we cannot exclude the possibility of some recall bias. There may be a discrepancy between what physicians say and report and how they behave. Indeed, there seems to be a discrepancy between the number of patients who were ventilated (see Table 1) and what their physicians say they would do in an exacerbation or for diurnal hypercapnia (see Table 2). Unfortunately we do not have the data needed to evaluate that issue. The study focused on NIV in patients with CF. Even if most of the adult CF centers also cared for adult patient with COPD, our survey had no

questions about NIV for COPD, so we cannot make any comparison of NIV in those 2 patient populations. The survey gives only a cross-sectional evaluation of NIV, so we did not collect any longitudinal data, such as the average duration of NIV use or the number of patients who discontinued NIV. Also, all the data reflect the prescriber's point of view, and our study design did not allow objective evaluation of patient adherence to NIV or problems with NIV.

### Conclusions

There is relative homogeneity in the indications and implementation on NIV in France. The centers have a relatively long list of expected NIV benefits, which contrasts with the fact that very few of the expected benefits have been validated. Future studies should assess NIV benefits. Finally, if we want to improve success with NIV, we have to pay more attention to patient comfort and quality of life.

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## Appendix

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