Defining successful non-invasive ventilation initiation: Data from a real-life cohort

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Original article

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SUMMARY AT A GLANCE: *(maximum 50 words).*

In this cohort, we have shown that, following NIV initiation, improvement in gas exchange was not correlated to improvement in quality of life and that side effects

were common and associated with poorer outcome. Achieving a tidal volume of 7.8ml/kg of ideal body weight increases the chance of adequate NIV initiation.

ABSTRACT:

Background: When home non-invasive ventilation (NIV) is initiated, 5 goals need to be achieved: a daily use > 4hours/day, an improvement in gas exchange, in health-related quality of life (HRQL), in sleep quality without significant side effects. Our aim was to assess how frequently these 5 goals were reached and the factors predictive of achievement.

Methods: Monocentric cohort study that included patients electively established on home NIV between 05/2017 and 08/2019. HRQL was assessed at baseline and follow-up by the Severe Respiratory Insufficiency questionnaire. Adequate initiation was defined as the achievement of at least 3 of 5 goals and successful initiation as the achievement of all of them.

Results: Two-hundred and fifty patients were included at baseline. Respiratory failure was due to: obesity hypoventilation syndrome (n:95; 38%), neuromuscular disease (n:70; 28%), chronic obstructive pulmonary disease (n:66; 26%) and chest-wall disease (n:19; 8%). At follow-up, measures of all 5 goals were available in 141 (56%) patients. Adequate NIV initiation was achieved in 96 (68%) patients. Only 12 (9%) patients achieved all goals. In multivariate analysis, a tidal volume ≥ 7.8ml/kg of ideal body weight was associated with an increased likelihood of adequate NIV initiation: HR: 5.765 [95%CI:1.824 - 18.223] (p=0.006). Improvement in daytime $PaCO_2$ was not correlated to improvement in HRQL or in sleep quality. Severe to very severe NIV related side effects occurred in 114 (47%) patients and were associated with higher daytime $PaCO_2$: 6.35±1.08kPa vs. 5.92±0.79 (p<0.001).

Conclusion: Successful home NIV initiation is rarely achieved in real-life. HRQL and NIV tolerance should be assessed to improve patient centred outcomes.

Short title: *What is a successful NIV initiation?*

Keywords: *non-invasive ventilation, chronic respiratory failure, quality of life, patient reported outcome, COPD*

INTRODUCTION:

Over the last decade, the use of home non-invasive ventilation (NIV) has increased (1). Its use is supported by randomised controlled trials for patients with chronic hypercapnic respiratory failure secondary to chronic obstructive pulmonary disease (COPD) (2,3), obesity hypoventilation syndrome (OHS) (4–8), amyotrophic lateral sclerosis (ALS) (9) and cystic fibrosis (10). When initiated, NIV should be used at least 4hours/day in order to improve survival (11).

The level of pressure delivered by the ventilator needs to normalize, or at least, reduce the level of carbon dioxide (2,3). Such reduction is particularly challenging to achieve in patients with COPD but less so in patients with OHS or neuromuscular disease as they only have respiratory muscle weakness whereas COPD patients also have damaged lungs.

Patients established on home NIV do not only use their ventilator to reduce their carbon dioxide but to improve their symptoms, their health-related quality of life (HRQL) and their quality of sleep. These patient centred-outcomes are particularly relevant in these patients that have a poor prognosis (11) and has NIV can worsen their HRQL (13). Several strategies such as polysomnographic titration (14) and automated NIV modes (15,16) have been assessed to improve HRQL and sleep quality, without success.

Ideally, we think that successful NIV initiation needs to achieve 5 goals (a) a decreased carbon dioxide level (b) an improvement in HRQL (c) an improvement in

sleep quality (d) an adherence to treatment of at least 4hours/day (e) without significant negative side effects. Adequate NIV initiation needs to achieve at least 3 of these 5 goals. To date, no study has reported the outcome of home NIV initiation using both physiological criteria (carbon dioxide level) and patient centred-outcomes in an unselected population of patients with chronic hypercapnic respiratory failure.

The main objective of our study was to assess how frequently successful (5 goals out of 5) and adequate (3 goals out of 5) NIV therapy was achieved at 8-weeks following NIV initiation. The secondary aims of our study were to identify predictive factors associated with adequate NIV initiation and to compare how frequently these goals were achieved in each diagnostic group.

METHODS:

We conducted a monocentric cohort study. The study was approved by the local ethic committee (approval 2020-300). Data were collected retrospectively from the institutional electronic medical record.

Inclusion criteria

We included all patients admitted for elective NIV initiation in Rouen University Hospital Respiratory Department between May 2017 and August 2019. Patients established on NIV following an acute exacerbation were excluded as well as those who did not attend follow-up (because of death or failure to attend any follow-up).

Patients included in the analysis were divided in 4 groups according to their underlying respiratory disease: (a) COPD group that included patients with COPD or other obstructive airway diseases with or without apnoeic events (b) OHS group that included patients with OHS with or without apnoeic events (c) neuromuscular disease (NMD) group that included patients with slowly or rapidly progressive NMD and (d) chest wall disease (CWD) group.

NIV initiation and follow-up

Patients referred for NIV initiation in our centre underwent a systematic evaluation that included: baseline type II overnight polysomnography (*ie* during unsupported breathing), daytime (*ie* from 10am to 6pm) arterial blood gas (ABG) sampling and end of night (*ie* 6am) ABG sampling, spirometry and a comprehensive respiratory review. Quality of life and of sleep were systematically assessed as part of patient clinical management prior to NIV initiation and at each follow-up visit using the

following questionnaires: the French translated Severe Respiratory Insufficiency questionnaire (SRI) (17) for HRQL and the Pittsburgh Sleep Quality Index (PSQI) (18) for sleep quality. We chose the SRI as it provides a multi-dimensional assessment of HRQL and has been developed and validated for patients with chronic respiratory failure (19–21). Following, these assessments, the decision to initiate home NIV was made by two senior respiratory consultants with expertise in the management of chronic respiratory failure (MP, ZG) according to criteria detailed in the online supplement (OLS)

NIV was initiated during an inpatient stay (eFigure 1 in OLS). Daytime acclimation of NIV was performed in all patients. Initial NIV settings were decided based on the underlying respiratory disease, the presence of apnoeic events and the severity of respiratory failure. Built-in humidifiers were used for all patients. Efficacy of NIV was assessed during the following morning by review of overnight oximetry and/or transcutaneous capnography, data from ventilator built-in software, end of night ABG and by assessing patient's tolerance. NIV adjustments protocol is detailed in OLS.

All patients received structured education on the use of their NIV during their inpatient stay. Additional education was provided in the home setting by the local home healthcare provider. All patients were instructed to use their NIV overnight. For patients with advanced diaphragmatic weakness (*ie* patients with amyotrophic lateral sclerosis) were asked to use their NIV also during the day.

Follow-up was planned 8-weeks following NIV initiation and included: respiratory review, HRQL and sleep quality questionnaires and, ABG during unsupported

breathing, and after 1-hour on NIV. NIV tolerance was assessed using a systematic questionnaire that included 11 NIV-related side-effects (eye redness, rhinorrhoea, mouth dryness, hoarseness, bloating, mask related pain, mask harness related pain, pressure sore, noticeable leaks, deventilation dyspnoea and, perceived patient-ventilator asynchrony). Each side effect was graded on a 0 to 4 scale as follow: absent (0), mild (1), moderate (2), severe (3) and intolerable or very severe (4). A significant side effect was defined as a side effect that as at least rated as severe (≥3 out of 4).

Outcomes

Successful NIV initiation was defined as the achievement of all of the following goals:

- Improvement in gas exchange was assessed by comparing daytime $PaCO_2$ during unsupported breathing before NIV initation and daytime $PaCO_2$ during unsupported breathing at follow-up visit. Successful improvement in gas exchange was defined as a follow-up $PaCO_2$ <6.5kPa, or a $PaCO_2$ that decreased by at least 0.5kPa or 20% from baseline.
- Improvement in HRQL was assessed by the change in the SRI score. Improvement was defined as an improvement superior or equal to the minimal detectable change (MDC) calculated in the study population as follow: MDC = 1.96 * standard error of measurement *square root of 2. MDC was established at 3.4 in our study population.
- Improvement in quality of sleep was defined as a decrease of 3 or more points in the PSQI when compared to baseline (22).

- Satisfactory use of NIV was defined as a mean usage of ≥ 4hours/day in the 30 days preceding follow-up assessment. Data were obtained from the ventilator built-in software.
- Satisfactory tolerance of NIV was defined as the absence of any severe or very severe (grade 3 and 4) NIV related side effect.

Adequate NIV initiation was defined as the achievement of at least 3 of any of the 5 above goals.

Statistical analysis

Data distribution was assessed using Shapiro-Wilk test. Continuous data are presented as mean and SD if normally distributed or median and interquartile if non-normally distributed. Categorical data are presented as frequency counts and percentages. Student T-test, ANOVA, Friedman, Mann-Whitney, Wilcoxon, chi-2 tests were used as appropriate. p-value were reported after Bonferroni correction for multiple tests when required. Correlations were assessed using Spearman correlation coefficient. Multivariate analysis was performed using binomial regression. Continuous data included in the regression model were dichotomized based on the median value of the entire study population. Only variables with a p-value <0.2 were included in the regression model. In the regression model, we did not include tidal volume or tidal volume/ body weight despite a p-value <0.2 as both were correlated to the tidal volume / ideal body weight. Tidal volume / ideal body weight variable was chosen as it had the lowest p-value in univariate analysis and because it was a more reliable parameter taking into account the wide range of weight in our study population. All tests were two-sided and type I error rate was set

at 0.05. Statistical analysis was performed using IBM SPSS Statistics v25.0 (IBM Corp, Armonk, New York, USA).

RESULTS:

Study population

From May 2017 to August 2019, 283 patients were admitted for elective NIV initiation. Of those, 250 (88%) attended follow-up evaluation (Figure 1). Underlying respiratory disease was: OHS (n:95; 38%), NMD (n:70; 28%), COPD (n:66; 26%) and CWD (n:19; 8%). Characteristics of the included patients are summarized in table 1. NIV titration was achieved in 3.7±1.1 days. End of night ABG sampling on NIV, data from the built-in software of the night prior to discharge and discharge settings are detailed in table 2. The majority of patients was set on an oro-nasal mask (n:231; 92%).

Follow-up

Follow-up was performed 9.2 [6.0 - 13.5] weeks following initial admission without difference between diagnostic groups (p=0.393). At follow-up, change in daytime $PaCO_2$ from baseline was evaluable in 241 (96%) patients and did not improved significantly: -0.11kPa [IC95%: -0.22 – 0.01] (p=0.063). However, after 1-hour of NIV, $PaCO_2$ decreased significantly: -0.67kPa [IC95%: -0.78 – -0.56] (p<0.001). Baseline and follow-up SRI and PSQI questionnaire were available for 198 (79%) and 163 (65%) patients respectively. At follow-up, improvement HRQL and quality of sleep was similar between diagnostic groups. Adherence to NIV was evaluated in 221 (88%) patients and was similar between diagnostic groups as well as the percentage of days with a use ≥ 4hours (p=0.661 and 0.681 respectively). Except for the respiratory rate (p=0.222), data from ventilator built-in software varied significantly between diagnostic groups (Table 3).

Side effects were assessed in 242 (97%) patients. Grade 3 or 4 side effects were : mouth dryness (n=77; 32%), noticeable leaks (n=42; 14%), eye redness (n=26; 11%) patients, rhinorrhoea (n=16; 7%), bloating (n=16; 7%), mask related pain (n=16; 7%), perceived patient-ventilator asynchrony (n=15, 16%), mask harness related pain (n=7; 3%), deventilation dyspnoea (n=7; 3%), pressure sore (n=6; 3%) and, hoarseness (n=4; 2%). Patients with at least one severe or very severe NIV related side effect had a lower HRQL at follow-up than those who did not: 53.6±16.8 vs. 58.6±15.8 (p=0.037), a poorer quality of sleep: 8.0±4.3 vs. 6.7±3.0 (p=0.034) and a higher follow-up $PaCO_2$: 6.35±1.08 vs. 5.92±0.79kPa (p<0.001). Adherence to treatment was similar at 5.6hrs/day (p=0.893).

Change in daytime $PaCO_2$ was not correlated to improvement in HRQL (rho=-0.011, p=0.885) or change in sleep quality (rho=-0.025, p=0.756) but was correlated to daily use of NIV (rho=-0.149, p=0.031). Change in HRQL was not correlated to daily use of NIV (rho=-0.133, p=0.075) or change in sleep quality (rho=0.104, p=0.189). Change in sleep quality was not correlated to daily use of NIV (rho=-0.064, p=0.440) (eFigure 2 and 3). Patients with an adherence > 4h/days were more likely to have an improvement in their PaCO2 (OR= 2.05 [95%CI: 1.04 – 3.93], p= 0.035). Patients with an improvement in their PaCO2 were more likely to have a satisfactory tolerance (OR= 2.09 [95%CI: 1.28 – 3.83], p= 0.021). Adherence or PaCO2 improvement did not increase the likelihood of an improved quality of life or sleep (eTable 3).

Quality of NIV initiation

The $PaCO_2$ reduction goal was achieved in 185 (77%) patients with a significant difference in the degree of reduction between each diagnostic group ($p<0.001$) (Figure 2). An adherence to treatment ≥ 4hours/days was achieved in 152 (69%) patients without significant between each diagnostic group ($p=0.737$). Improvements were achieved in HRQL in 117 (59%) patients, in sleep quality in 63 (39%) patients, and a satisfactory tolerance of NIV was seen in 129 (53%) patients, without any significant difference between diagnostic groupings.

Assessment of all 5 NIV goals were available in 141 (56%) patients. Adequate NIV initiation defined by the achievement of at least 3 goals of 5 NIV goals was obtained in 96 (68%) of patients without significant between each diagnostic group ($p=0.345$). Successful NIV initiation defined by the achievement of all goals was obtained in 12 (9%) patients.

Predictive factors associated to adequate NIV initiation

Patients that achieved adequate NIV initiation had a milder severity disease than those who did not (Online supplement eTable 1). In multivariate analysis, an adequate NIV initiation was less likely to occur in patients with a dyspnoea ≥ 3 on the mMRC scale. Adequate NIV initiation was more likely to occur when overnight estimated tidal volume was ≥ 7.8ml/kg of ideal body weight (Table 4).

DISCUSSION:

In our study, we have shown that adequate NIV initiation was achieved in 68% of our cohort but only 9% of patients met all the goals of a successful NIV initiation. We found no correlation between the improvement in $PaCO_2$ and quality of life, or quality of sleep. We've also shown that severe side effects were commonly reported by patients and were associated to an impaired quality of life, quality of sleep and poorer control of daytime $PaCO_2$. Finally, we've identified that achieving a tidal volume of at least 7.8ml/kg of ideal body weight was associated with an increased chance of adequate NIV initiation.

In our study population, we failed to achieve a significant reduction in daytime $PaCO_2$ during unsupported breathing at follow-up. This result could suggest that patients were not sufficiently ventilated. We do not believe that it was the case. We explain such result can be explained by the fact that: (a) the follow-up ABG was performed 9 weeks following NIV initiation which may not allow sufficient time for CO_2 to normalize especially in COPD and OHS patients (3,12,23–25) (b) some patients in the NMD group did not have daytime hypercapnia but only end of night hypercapnia ; in these, NIV was initiated based on symptoms and lung function tests (c) some patients in the NMD group had a rapid progression of their muscle weakness that would have prevented a significant improvement in $PaCO_2$ (d) we were able to show a significant reduction in end of night $PaCO_2$ with the use of NIV during baseline titration and a significant reduction of $PaCO_2$ following one-hour on NIV at follow-up. Similar night-time reductions were seen in another real-life cohort (26).

Despite inpatient initiation, 47% of our cohort reported grade 3 or 4 NIV side effects. Amongst these, mouth dryness was most commonly reported, similar to previous cohorts (20,27). This occurred despite the use of a built-in humidifier for all patients. These side effects were associated with poorer control of $PaCO_2$, worse quality of life and sleep quality but were not associated with a lower adherence to NIV. This result outlines the fact NIV side effects should be closely monitored and addressed.

Our large cohort allowed us to identify factors associated with an increased chance of adequate NIV initiation. Amongst those, in multivariate analysis, an estimated tidal volume ≥ 7.8ml/kg of ideal body weight is of particular interest. Monitoring of data provided by ventilator built-in software is recommended (28) and is increasingly used for remote monitoring (29). Our results identify a target that can be remotely monitored easily and that is applicable in a heterogenous population of patients with a wide range of weights. This may facilitate remote NIV initiation without the use of transcutaneous capnography home monitoring. It may also help NIV centres to face the increasing numbers of patients with chronic respiratory (30,31) failure especially during the COVID-19 pandemic (32).

In our study, we did not find any correlation between improvement in HRQL, quality of sleep and improvement in $PaCO_2$ (eFigure 2-3 and eTable 2). Improvement in $PaCO_2$ was significantly but poorly correlated to treatment adherence (rho:-0.149). This result highlights the fact that there is no direct link between $PaCO_2$ control and patients centred outcomes. This result illustrates the complexity of NIV initiation and the requirement of a multidimensional approach to assess its benefits. Such an approach could help individualise the goals for each patient. This would allow the

prioritization of carbon dioxide reduction in some cases (COPD patients for an example) while an improvement in patient-centred outcomes would be the goal in others (ALS patients for an example).

In our cohort, 68% of our patients achieved 3 out of the 5 predefined goals for successful NIV initiation but only 9% achieved all goals. This occurred in a centre experienced in NIV initiation, using inpatient initiation and with home visits performed by a homecare provider (at least 2 before the first follow-up appointment). A lower adherence to treatment or more side effects may occur in healthcare organizations in which NIV initiation and follow-up are organised differently.

Our study has several limitations. Firstly, we included patients with chronic respiratory failure caused by diverse respiratory diseases. This led to a heterogeneity in the study population but also reflects real-life practice. Secondly, given the retrospective design of our study, we were able to assess our primary outcome only in 56% of our initial cohort. Finally, we assessed the outcome of patients at their first follow-up. As NIV is a challenging treatment to adjust to, more benefit may have occured in later evaluations. However, in clinical trials, improvement is usually seen at the first follow-up (3,9,20,33).

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Dr. Jolly has nothing to disclose

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Table 1: Study population characteristics. Results expressed as n (%), median [interquartile] and mean (standard deviation) were appropriate. (COPD: Chronic Obstructive Pulmonary Disease; NMD: Neuromuscular disease; OHS: Obesity Hypoventilation Syndrome; CWD: Chest wall disease; HRQL: Health-related quality of life; P/Y: Pack-years; $PaCO_2$: Partial arterial carbon dioxide pressure; mMRC : modified Medical Research Council ; FEV1 : Forced expired volume at 1 second ; FVC : Forced vital capacity ; $Sat0_2$: Oxygen saturation ; $TcCO_2$: Transcutaneous carbon dioxide pressure ; SRI : Severe Respiratory Insufficiency ; PSQI : Pittsburgh Sleep Quality Index, *: within group comparison with COPD as reference).

	Study population (n=250)	**COPD (n=66)**	**NMD (n=70)**	**OHS (n=95)**	**CWD (n=19)**	p
Gender (male)	130 (52.0)	39 (59.1)	42 (60.0)	42 (44.2)	7 (36.8)	0.067
Age (years)	65.1 [54.3 - 74.2]	66.1 [59.7 - 74.8]	64.9 [48.2 - 72.2]	64.7 [54.3 - 73.7]	64.2 [47.6 - 80.3]	0.233
Former smoker	113 (72.0)	48 (76.2)	23 (74.2)	37 (64.9)	5 (83.3)	0.547
Tobacco consumption (P/Y)	30 [16 - 50]	40 [30 - 56.5]	16 [7.9 - 37.3]*	30 [17.3 - 45]*	5.8 [3.3 - 18.3]	<0.001
Body mass index (kg/m^2)	29.2 [23.0 - 36.9]	26.3 [21.8 - 31.3]	24.1 [20.6 - 28.9]*	37.6 [33.6 - 44.1]*	23.1 [19.5 - 27.7]	<0.001
Neck circumference (cm)	42 [38 - 46]	42 [37.8 - 45]	38.5 [36.5 - 41]*	45 [42 - 50.5]*	38.5 [36.8 - 41.5]	<0.001
Dyspnoea (mMRC)	3 [2 - 3]	3 [2.5 - 4]	2 [0 - 3]*	3 [2 - 3]*	2 [1 - 3]	<0.001
Phlegm production	63 (25.7)	29 (45.3)	10 (14.5)	22 (23.7)	2 (10.5)	<0.001
Chronic cough	104 (42.3)	37 (57.8)	22 (31.4)	37 (39.8)	8 (42.1)	0.019
Lung function tests						
FEV1 (L)	1.38 [0.88 - 1.94]	0.82 [0.66 - 1.4]	1.5 [1.04 - 2.16]*	1.73 [1.35 - 2.29]*	1.13 [0.75 - 1.35]	<0.001
FEV1 (% predicted)	55 [38.85 - 76]	34.5 [27.4 - 49]	64 [44 - 79.3]*	70.5 [52.3 - 90.9]*	48 [36 - 57]	<0.001
FVC (L)	1.94 [1.39 - 2.67]	1.87 [1.37 - 2.47]	1.86 [1.24 - 2.53]*	2.24 [1.64 - 3.01]*	1.33 [0.99 - 1.56]	<0.001
FVC predicted (% predicted)	63 [48.4 - 81]	61.2 [49.5 - 72]	60.5 [46 - 82.3]*	75 [55.2 - 92.8]*	52 [33.9 - 60]	<0.001
FEV1/FVC	75.87 [62.9 - 85]	52 [41.7 - 63.5]	83.4 [77.5 - 89.6]*	76.8 [71.9 - 84.5]*	83.8 [72 - 93.6]	<0.001
Unsupported breathing arterial blood gas						
Daytime $PaCO_2$ (kPa)	6.06 [5.60 - 6.64]	6.70 [6.11 - 7.37]	5.70 [5.1 - 6.2]*	6.11 [5.76 - 6.5]*	6.20 [5.79 - 6.64]	<0.001
End of night $PaCO_2$ (kPa)	6.75 [6.15 - 7.40]	7.36 [6.79 - 8.33]	6.18 [5.74 - 6.86]*	6.77 [6.3 - 7.41]*	6.88 [6.23 - 7.1]	<0.001
Baseline overnight sleep study						
Apnoea-hypopnoea index (/h)	18 [5 - 37]	13 [7 - 26.8]	15 [8 - 28]	40.9 [28 - 68]*	17 [4 - 27]	<0.001
Time spent with Sat02 <90% (%)	26 [12 - 45]	83.5 [21.3 - 94.3]	12 [0 - 43]*	66 [29.8 - 94]	12 [3.5 - 93.5]*	<0.001
Overnight mean TcC02 (kPa)	6.43 [5.72 - 7.14]	6.67 [6.1 - 7.72]	6.38 [5.46 - 6.94]*	6.48 [5.71 - 7.18]	6.14 [5.18 - 7.26]	<0.001
Overnight maximal TcC02 (kPa)	7.3 [6.52 - 8.35]	8 [6.53 - 8.9]	6.84 [6.43 - 7.87]	7.1 [6.66 - 8.1]	7.09 [6.19 - 8.37]	<0.001
Baseline HRQL questionnaire						
SRI summary scale (/100)	50.6 [39.2 - 62.3]	50.4 [39.9 – 62.5]	58.0 [43.8 - 66.8]	52.2 [40.1 - 63.3]	51.5 [43.0 - 69.2]	0.493
PSQI (/24)	9 [5 - 13]	10 [5.5 - 14]	8 [5 - 11]	10 [7 - 14]	8.5 [5.3 - 13.5]	0.116

Table 2: Outcome of NIV initiation with data on the night prior to discharge and discharge NIV settings. Results expressed as n (%), median [interquartile] and p-value in bold indicates significant difference (NIV: Non-invasive ventilation; COPD: Chronic obstructive pulmonary disease; NMD: Neuromuscular disease; OHS: Obesity hypoventilation syndrome; CWD: Chest wall disease; $Sat0_2$: Saturation on oxygen; $TcCO_2$: Transcutaneous carbon dioxide pressure; $PaCO_2$: Partial arterial carbon dioxide pressure ; IPAP: Inspiratory positive airway pressure; EPAP: Expiratory positive airway pressure ; PC: Pressure Control ; PS: Pressure support ; Vol: Volume-targeted pressure support ventilation, *: within group comparison with COPD as reference)

	Study population (n=250)	**COPD (n=66)**	**NMD (n=70)**	**OHS (n=95)**	**CWD (n=19)**	p
NIV initiation duration (days)	4 [3 - 5]	4 [3 - 5]	4 [3 - 5]	4 [3- 5]	4 [3- 5]	0.128
Data from overnight monitoring before discharge						
End of night PaCO2 on NIV (kPa)	6 [5.40 - 6.53]	6.3 [5.55 - 6.81]	5.6 [4.84 - 6]*	6.18 [5.86 - 6.62]	6.25 [5.4 - 6.9]	**<0.001**
Estimated tidal volume (ml)	498 [380 - 609.5]	516.5 [462 - 660]	413 [350 - 520]*	536 [398 - 621]	415 [280 - 611]*	**<0.001**
Tidal volume / body weight (ml/kg)	5.85 [4.75 - 7.68]	7.35 [5.751 - 8.89]	6.21 [5.13 - 7.93]	4.83 [4.31 - 5.85]*	6.80 [4.67 - 10.53]	**<0.001**
Tidal volume / ideal body weight (ml/kg)	7.86 [6.17 - 9.20]	8.30 [7.52 - 9.92]	6.71 [5.69 - 7.83]*	8.37 [6.45 - 9.40]	7.75 [4.31 - 10.12]	**<0.001**
Respiratory rate (cycle/min)	16 [14 - 17.8]	15 [14 - 17]	16 [14 - 17]	16 [14.61 - 17.3]	18 [15 - 21]	**0.025**
Triggered breaths (%)	48.0 [24.1 - 72.0]	56 [27.41 - 76.5]	40 [16.6 - 70]*	38.99 [20.5 - 66.55]*	64.5 [52 - 87]	**0.008**
Estimated residual events (/h)	5.1 [1.6 – 11.0]	4.3 [1.2 - 7.9]	5.4 [1.6 - 15]*	6.6 [2.2 - 11.1]*	3.1 [0.6 - 7.6]	**0.016**
Median unintentional leaks (L/min)	7.9 [1.0 - 18.7]	7.7 [0 - 15.66]	4.77 [0 - 14.76]	8.18 [1.2 - 18.59]	12.6 [4.8 - 20.4]	0.500
3% Oxygen desaturation index (/h)	5 [1.6 - 11]	7.8 [3.84 - 11]	4.2 [1.86 - 9]	10.47 [6 - 21]	10 [5 - 14]	**0.003**
Time spent with Sat02 <90% (%)	3 [0 - 24]	1.5 [0 - 7.1]	1.8 [0 - 14]	8.8 [1 - 44.9]	1 [0 - 8]	0.119
Overnight mean TcC02 (kPa)	6.14 [5.6 - 6.85]	6.32 [5.6 - 7.1]	6.05 [5.57 - 6.72]	6.13 [5.61 - 6.9]	6.53 [6.08 - 6.92]	0.425
Overnight maximal TcC02 (kPa)	7.2 [6.51 - 8]	7.25 [6.32 - 8.22]	7.03 [6.4 - 7.73]	7.08 [6.72 - 7.87]	7.46 [6.8 - 8.4]	0.260
Discharge NIV settings						
PS / PC / Vol (n)	218 / 2 / 30	63 / 0 / 3	63 / 1 / 6	75 / 0 / 20	17 / 1 / 1	**0.020**
IPAP (cmH20)	18 [16 - 22]	20 [18 - 22]	16 [12 - 19]*	22 [20 - 26]*	16 [14 - 20]*	**<0.001**
EPAP (cmH20)	6 [4 - 8]	6 [4 - 8]	4 [4 - 8]	9 [8 - 10]*	4 [4 - 6]	**<0.001**
Backup rate (per minute)	14 [14 - 14]	14 [12 - 14]	14 [14 - 16]*	14 [14 - 16]*	14 [14 - 14]	**<0.001**
Additional oxygen (yes). n (%)	0 [0 - 1]	1 [0 - 2]	0 [0 - 0]	0 [0 - 2]	0 [0 - 1]	**<0.001**

Table 3: Change in arterial CO_2, quality of life and quality of sleep from baseline to follow-up and data from ventilator built-in software at follow-up. Results expressed as n (%), median [interquartile] and p-value in bold indicates significant difference (NIV: Non-invasive ventilation; COPD: Chronic obstructive pulmonary disease; NMD: Neuromuscular disease; OHS: Obesity hypoventilation syndrome; CWD: Chest wall disease; $PaCO_2$: Partial arterial carbon dioxide pressure; SRI: Severe respiratory insufficiency questionnaire; PSQI: Pittsburgh Sleep Quality Index, *: within group comparison with COPD as reference)

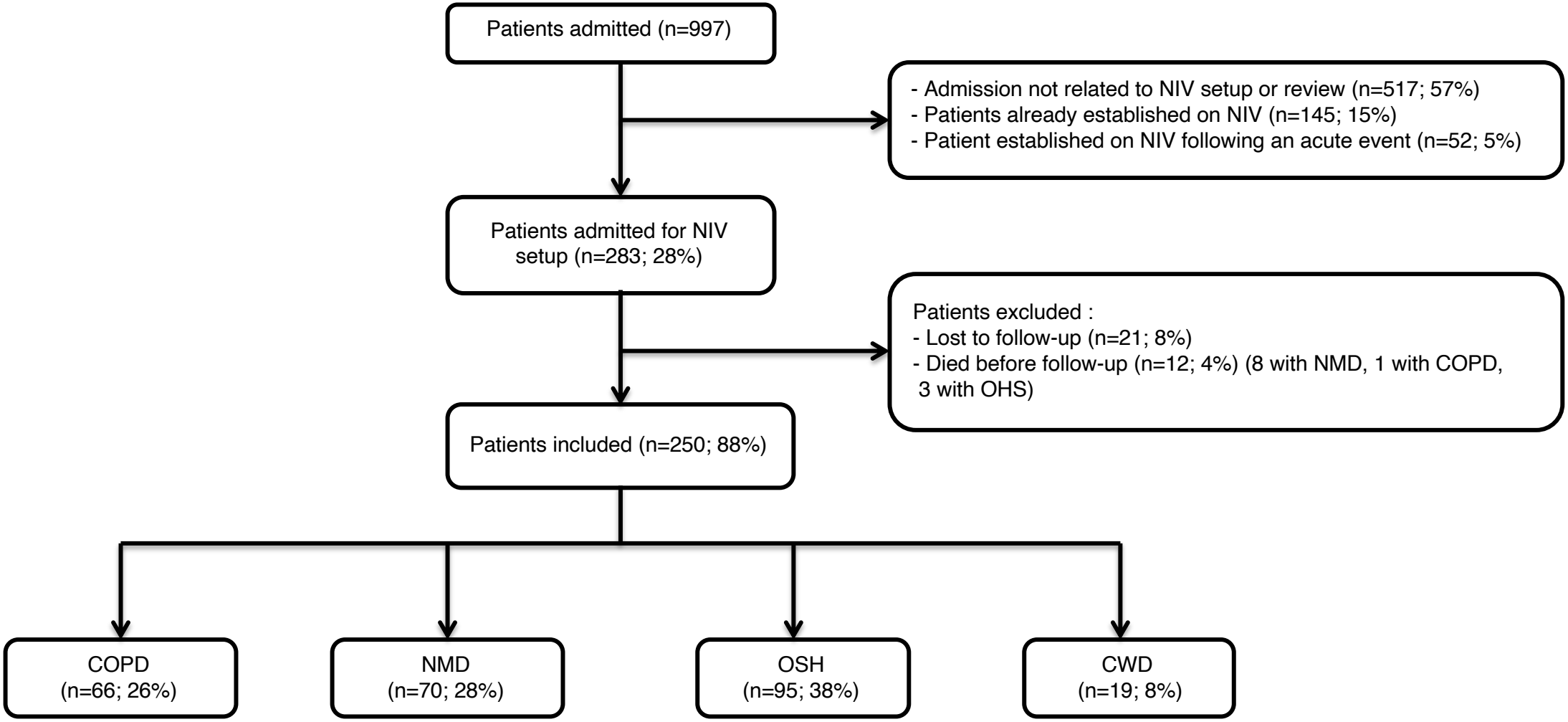
	Study population	**COPD**	**NMD**	**OHS**	**CWD**	p
Change in daytime PaCO2 (kPa) (n=241)	0.00 [-0.51 - 0.40]	0.04 [-0.40 - 0.59]	0.10 [-0.37 - 0.5]	-0.21 [-0.58 - 0.24]	0.24 [-0.1 - 0.47]	**0.028**
Change in SRI summary scale (/100) (n=198)	8.1 [-5.8 - 18.3]	7.4 [-2 - 17.9]	4.3 [-7.2 - 16]	8.6 [-8.2 - 20.1]	16.8 [-1.9 - 23.3]	0.306
Change in PSQI (/24) (n=163)	-1 [-5 - 1]	-1 [-6 - 0.8]	-1 [-4 - 0.5]	-1 [-4.3 - 1]	-3 [-6 - 0.8]	0.847
Adherence (h/day) (n=221)	5.86 [3.37 - 7.75]	6.08 [3.22 – 7.42]	6.28 [3.87 - 8]	5.45 [3.18 - 7.77]	5.62 [2.68 – 8.05]	0.661
Usage ≥ 4 hours per day (%) (n=221)	80 [36 - 100]	86.9 [46.8 - 100]	74.5 [17 - 96.8]	75 [36 - 96.9]	70 [54 - 90]	0.681
Estimated tidal volume (ml) (n=221)	500 [400 - 600]	540 [440 - 645.5]	465.5 [380 - 550]*	540 [400 - 620]	385 [280 - 489]*	**<0.001**
Respiratory rate (cycle/min) (n=221)	16 [14 - 18]	16.5 [14 - 18]	16 [14 - 18]	16 [14.35 - 18]	17 [16 - 19]	0.224
Triggered breaths (%) (n=221)	50 [23 - 75.5]	64 [33 - 87.54]	29.8 [15 - 69]*	46 [24 - 71]	64 [38.5 - 93]	**0.001**
Unintentional leaks (L/min) (n=221)	8.1 [1 - 26.6]	4.9 [0 - 17.6]	5.2 [1 - 12]	16.27 [6.6 - 40]*	1.2 [0 - 9]	**<0.001**
Estimated residual events (/h) (n=221)	4.0 [1.0 – 9.6]	2.1 [0.1 – 5.4]	6.0 [1.5 – 13.0]*	4.5 [1.6 – 10.5]*	1.4 [0.0 – 6.0]	**0.002**
Overnight breaks from NIV (n) (n=221)	0.5 [0 - 1]	0.08 [0 - 1]	0 [0 - 1]	1 [0 - 2]*	0.7 [0 - 3]	**0.024**

Table 4: Factors associated with adequate NIV initiation defined as the achievement of at least 3 of 5 predefined goals following NIV initiation. p-value in bold indicates significant difference. (BMI: Body mass index; mMRC: modified medical research council; FEV1: Forced expired volume at 1 second; ODI : Oxygen desaturation index ; $TcCO_2$: Transcutaneous carbon dioxide pressure ; $PaCO_2$: Partial arterial carbon dioxide pressure)

	Univariate analysis		**Multivariate analysis**	
	HR [95%CI]	p	HR [95%CI]	p
Gender (male)	1.646 [95%CI:1.009 - 2.687]	**0.043**	1.851 [95%CI:0.635 - 5.393]	0.259
BMI (≥ 29.6kg/m^2)	0.730 [95%CI:0.442 - 1.208]	0.214	*Not included*	
Dyspnoea (≥3mMRC)	0.620 [95%CI:0.352 - 1.094]	0.084	0.126 [95%CI:0.035 - 0.455]	**0.002**
Phlegm production (yes)	0.642 [95%CI:0.395 - 1.042]	0.086	0.329 [95%CI:0.097 - 1.113]	0.074
FEV1 (≥1.38L)	1.459 [95%CI:0.894 - 2.381]	0.131	2.011 [95%CI:0.712 - 5.684]	0.187
3% ODI (≥26/h)	0.717 [95%CI:0.408 - 1.260]	0.241	*Not included*	
Mean saturation (≥89%)	1.112 [95%CI:0.650 - 1.900]	0.700	*Not included*	
Overnight TcCO2 (≥6.41kPa)	0.900 [95%CI:0.445 - 1.820]	0.768	*Not included*	
Daytime PaCO2 (≥6.13kPa)	0.730 [95%CI:0.442 - 1.208]	0.214	*Not included*	
Tidal volume (≥500ml)	1.702 [95%CI:1.023 - 2.829]	0.039	*Not included*	
Tidal volume/body weight (≥5.9ml/kg)	1.493 [95%CI:0.891 - 2.502]	0.124	*Not included*	
Tidal volume/ideal body weight (≥7.8ml/kg)	1.827 [95%CI:1.084 - 3.081]	**0.021**	5.765 [95%CI:1.824 - 18.223]	**0.006**
Respiratory rate (≥16/min)	0.578 [95%CI:0.321 - 1.040]	0.061	0.352 [95%CI:0.112 - 1.105]	0.074
Triggered breath (≥48%)	0.699 [95%CI:0.408 - 1.200]	0.190	0.430 [95%CI:0.139 - 1.327]	0.142
Unintentional Leaks (≥7.8L/min)	0.855 [95%CI:0.508 - 1.440]	0.554	*Not included*	
Residual events (≥5.1/h)	1.118 [95%CI:0.648 - 1.929]	0.689	*Not included*	

Figure 1: Study flow-chart (NIV: Non-invasive Ventilation; COPD: Chronic obstructive pulmonary disease; NMD: Neuromuscular disease; OHS: Obesity hypoventilation syndrome; CWD: Chest wall disease)

Figure 2: Proportion of patients for which specific NIV goals were achieved for each diagnostic group (*: $p<0.05$). A significant side effect was defined as a side effect that rated as at least severe (≥3 out of 4). (NIV: Non-invasive Ventilation; COPD: Chronic obstructive pulmonary disease; NMD: Neuromuscular disease; OHS: Obesity hypoventilation syndrome; CWD: Chest wall disease; HRQL:Health-related quality of life; $PaCO_2$: Partial arterial carbon dioxide pressure)


Patients admitted (n=997)
- Admission not related to NIV setup or review (n=517; 57%)
- Patients already established on NIV (n=145; 15%)
- Patient established on NIV following an acute event (n=52; 5%)
Patients admitted for NIV setup (n=283; 28%)
Patients excluded :
- Lost to follow-up (n=21; 8%)
- Died before follow-up (n=12; 4%) (8 with NMD, 1 with COPD, 3 with OHS)
Patients included (n=250; 88%)
COPD (n=66; 26%)
NMD (n=70; 28%)
OSH (n=95; 38%)
CWD (n=19; 8%)


Improvement in PaCO2*
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Improvement in HRQL
Improvement in sleep quality
Adherence ≥ 4h/day
Lack of significant side effect
COPD
NMD
OHS
CWD

Online supplement of "Defining successful NIV setup: data from a real-life cohort"

Grégoire Jolly, Léa Razakamanantsoa, Emeline Fresnel, Zouhaier Gharsallaoui, Antoine Cuvelier, Maxime Patout

Methods:

Decision to initiate NIV

Decision to initiate NIV was made according to the underlying disease, patients' daytime and nighttime symptoms, $PaCO_2$, results from overnight polygraphy and, when appropriate results from lung function tests.

For patients with COPD in the absence of concomitant sleep apnea, NIV was initiated in patients with a PaCO2 > 7kPa in stable state or 2 to 4 weeks following an acute exacerbation. For patients with COPD and concomitant sleep apnea, NIV was initiated in patients with a PaCO2 > 6.5kPa. For patients with obesity hypoventilation syndrome, NIV was initiated in patients with PaCO2 > 6kPa if they had previous history of acute respiratory failure or if they were already treated by continuous positive airway pressure. For patients with neuromuscular disease, NIV was initiated in patients with PaCO2 >6kPa or if patients exhibit daytime dyspnea, orthopnea or had a forced vital capacity <50%. For patients with chest-wall disease, NIV was initiated in patients with PaCO2 > 6kPa or had a forced vital capacity <50%.

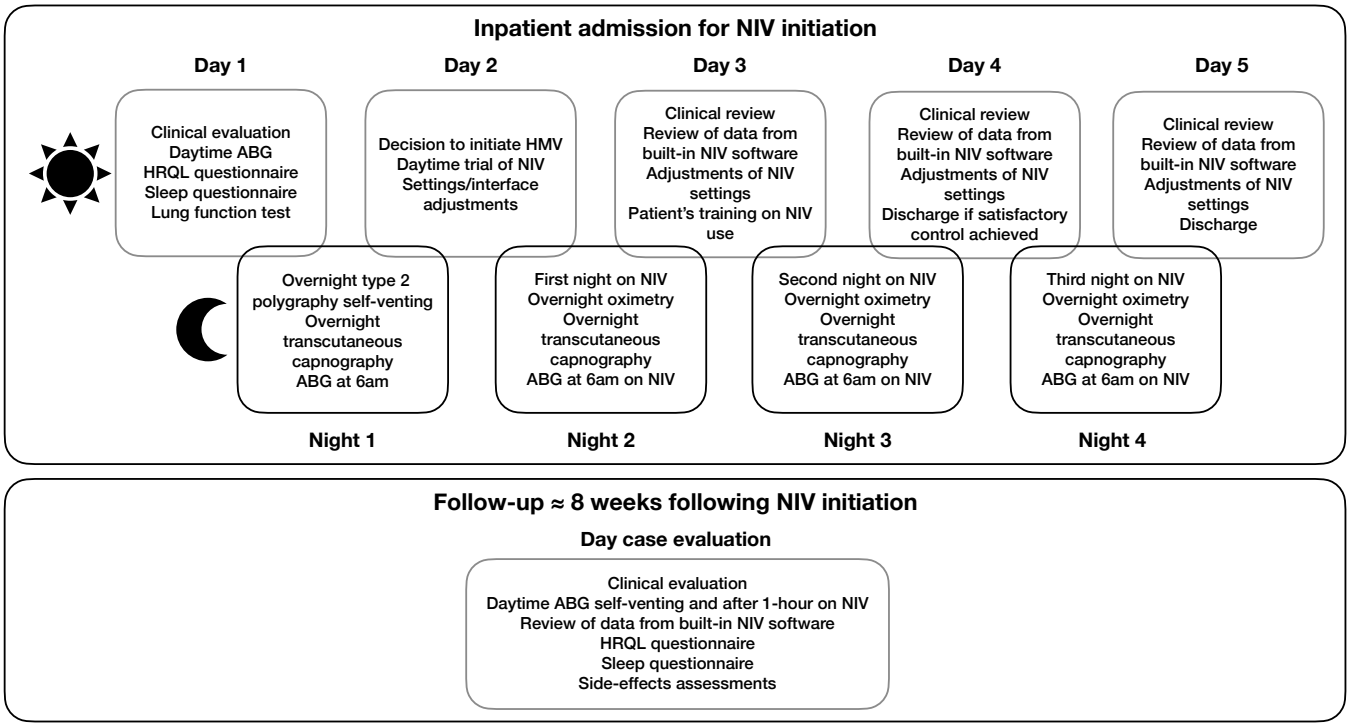
NIV initiation

NIV initiation was performed during an inpatient stay which was organized as described in eFigure 1.

Adjustments in NIV settings were made following clinical evaluation, review of overnight monitoring and in the absence of significant leaks. If reduction in PaCO2 was not sufficient or if residual nocturnal hypoventilation was seen, inspiratory pressure was increased by 2cmH2O. In some cases, such as a low percentage of triggered breaths or a high tidal volume, back-up respiratory rate was increased by +2breaths/min (with a maximal limit of 16breaths per minutes in COPD patients, and 20 in other diagnostic

groups). If apneic events occurred (desaturation index >10/h), positive expiratory pressure was increased by 2cmH2O with constant pressure support. If leaks were significant, a change of the interface was decided. If no improvement was seen, inspiratory pressure was decreased.

For patients already treated with long-term oxygen therapy, oxygen was added to the NIV at the same flow rate as daytime. In patients without long-term oxygen therapy, oxygen was only added if despite satisfactory control of hypoventilation, overnight mean



saturation was below 88% in COPD patients and 90% in others.

eFigure 1: Patient pathway for NIV initiation (ABG: arterial blood gas, HRQL: health-related quality of life; NIV: noninvasive ventilation)

Results:

Underlying respiratory disease

Patients in the neuromuscular disease group had the following underlying respiratory disease: amyotrophic lateral sclerosis (n=38; 56%), diaphragm palsy (n=8;12%); type I myotonic dystrophy (n=6; 9%), Duchenne's muscular distrophy (n=5; 7%); multiple sclerosis (n=3; 4%) or other slowly progressive neuromuscular disease (n=8; 12%). Patients in the chest-wall disease group had the following underlying respiratory disease: interstitial lung disease (n=9; 41%); kyphoscoliosis (n=8; 36%); post-tuberculosis (n=3; 14%) and undermined restrictive disease (n=2; 9%).

	Non-adequate NIV setup (n:45, 32%) n (%) / Med [Interquartile]	Adequate NIV setup (n:96; 68%) n (%) / Med [Interquartile]	p
Gender (male)	19 (42)	58 (60)	0.043
Age (years)	66.2 [56.3 - 71.8]	66.1 [59.7 - 74.8]	0.824
Former smoker	28 (31)	61 (69)	0.880
Tobacco consumption (P/Y)	35.5 [25 - 60]	36 [16 - 50]	0.275
Body mass index (kg/m^2)	32.43 [25.5 - 39]	29.78 [24.35 – 38.5]	0.162
Neck circumference (cm)	43 [38 - 48]	42 [39 - 46]	0.322
Dyspnoea (mMRC)	3 [2 - 4]	3 [2 - 3]	0.044
Phlegm production	15 (44)	19 (56)	0.086
Chronic cough	23 (38)	38 (62)	0.190
Underlying respiratory disease			
COPD	12 (34)	23 (66)	0.345
NMD	9 (23)	30 (77)	
OSH	22 (39)	35 (61)	
CWD	2 (20)	8 (80)	
Lung function tests			
FEV1 (L)	1.32 [0.88 - 1.86]	1.68 [1.16 – 2.09]	0.052
FEV1 (% predicted)	51.55 [38.4 - 76]	61 [46 - 80]	0.714
FVC (L)	1.86 [1.34 - 2.34]	2.29 [1.54 - 2.85]	0.419
FVC predicted (% predicted)	63 [45 - 80]	70 [54 - 83]	0.449
FEV1/FVC	76.49 [66.3 – 83.6]	76.32 [64 - 85]	0.721
Self-venting arterial blood gas			
Daytime $PaCO_2$ (kPa)	6.4 [5.9 – 7.31]	6.15 [5.56 – 6.56]	0.017
Wake $PaCO_2$ (kPa)	6.95 [6.23 - 7.86]	6.67 [6.18 - 7.31]	0.271
Self-venting overnight sleep study			
Apnoea-hypopnoea index (/h)	25 [10 - 40]	17.5 [6 - 36]	0.292
3% Oxygen desaturation index (/h)	34.5 [13 - 79]	25 [13 - 39]	0.087
Time spent with Sat02 <90% (%)	56 [16 - 95]	43 [7 - 87]	0.113
Overnight mean SatO2 (%)	89 [82 - 91]	90 [86 - 92]	0.032
Overnight mean TcC02 (kPa)	6.73 [6.16 - 7.8]	6.48 [5.74 - 7.25]	0.000
Overnight maximal TcC02 (kPa)	7.7 [6.67 - 8.46]	7.3 [6.45 - 8.4]	0.130
Baseline HRQL questionnaire			
SRI summary scale (/100)	50.93 [41.09 – 62.37]	50.86 [37.35 – 59.3]	0.463
PSQI (/24)	9 [5 - 11]	10 [6 - 13]	0.342
Data from NIV built-in software from the night prior to discharge			
Estimated tidal volume (ml)	470.5 [380 - 577.5]	545 [428.9 - 630]	0.020
Tidal volume / body weight (ml/kg)	5.4 [4.18 – 6.71]	6.15 [5.23 – 8.28]	0.006
Tidal volume / ideal body weight (ml/kg)	7.48 [6.2 – 9.21]	8.37 [6.82 – 10.12]	0.061
Respiratory rate (cycle/min)	16.65 [15 - 18.1]	15 [14 - 17]	0.005
Triggered breaths (%)	48.4 [35.2 - 77]	39.6 [22.5 – 66.55]	0.100
Estimated residual events (/h)	4.9 [1.9 - 11.7]	6.2 [2.1 – 11.8]	0.733
Unintentional leaks (L/min)	10.55 [4 - 20.6]	9.6 [1- 29.68]	0.778
Discharge NIV settings			
Pressure support (cmH20)	12 [9 - 15]	10 [8 - 14]	0.324
IPAP (cmH20)	20 [18 - 24]	20 [16 - 24]	0.663
EPAP (cmH20)	8 [6 - 10]	6 [4 - 8]	0.132
Backup rate (cycle/min)	14 [14 - 14]	14 [14 - 16]	0.320

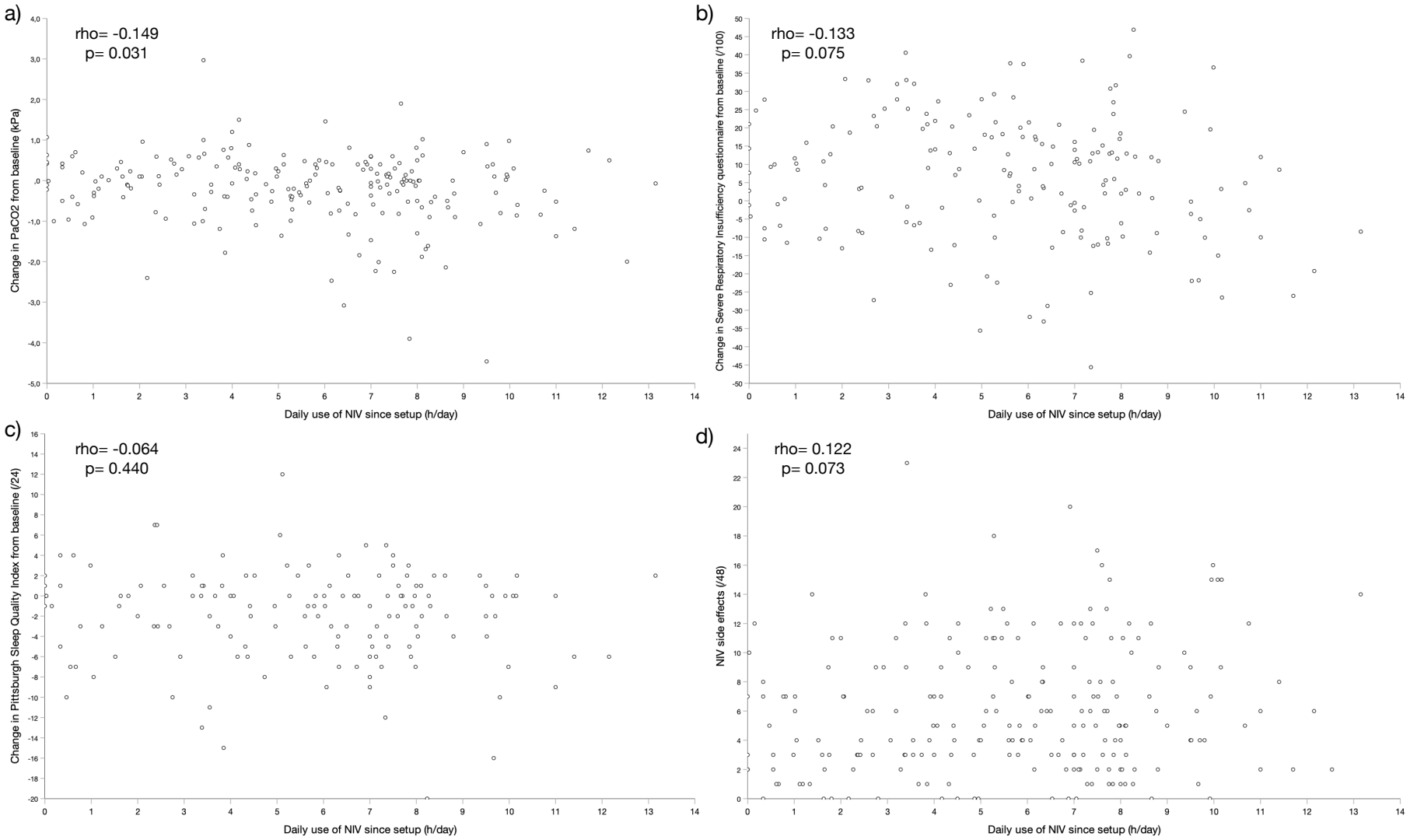
eTable 1: Comparison of population characteristics according to the achievement of an adequate NIV setup defined as the achievement of at least 3 out of 5 goals following NIV initiation. (COPD: Chronic Obstructive Pulmonary Disease; NMD: Neuromuscular disease; OHS: Obesity Hypoventilation Syndrome; CWD: Chest wall disease; HRQL:Health-Related Quality of Life; P/Y: Pack by years; PaCO2: Partial arterial carbon dioxide pressure; mMRC : modified Medical Research Council; FEV1 : Forced expired volume at 1 second; FVC : Forced vital capacity; Sat02 : Oxygen saturation; TcCO2 : Transcutaneous carbon dioxide pressure; SRI : Severe Respiratory Insufficiency; PSQI : Pittsburgh Sleep Quality Index; NIV: Non Invasive Ventilation; IPAP: Inspiratory positive airway pressure; EPAP: Expiratory positive airway pressure)

Correlation between goals at follow-up

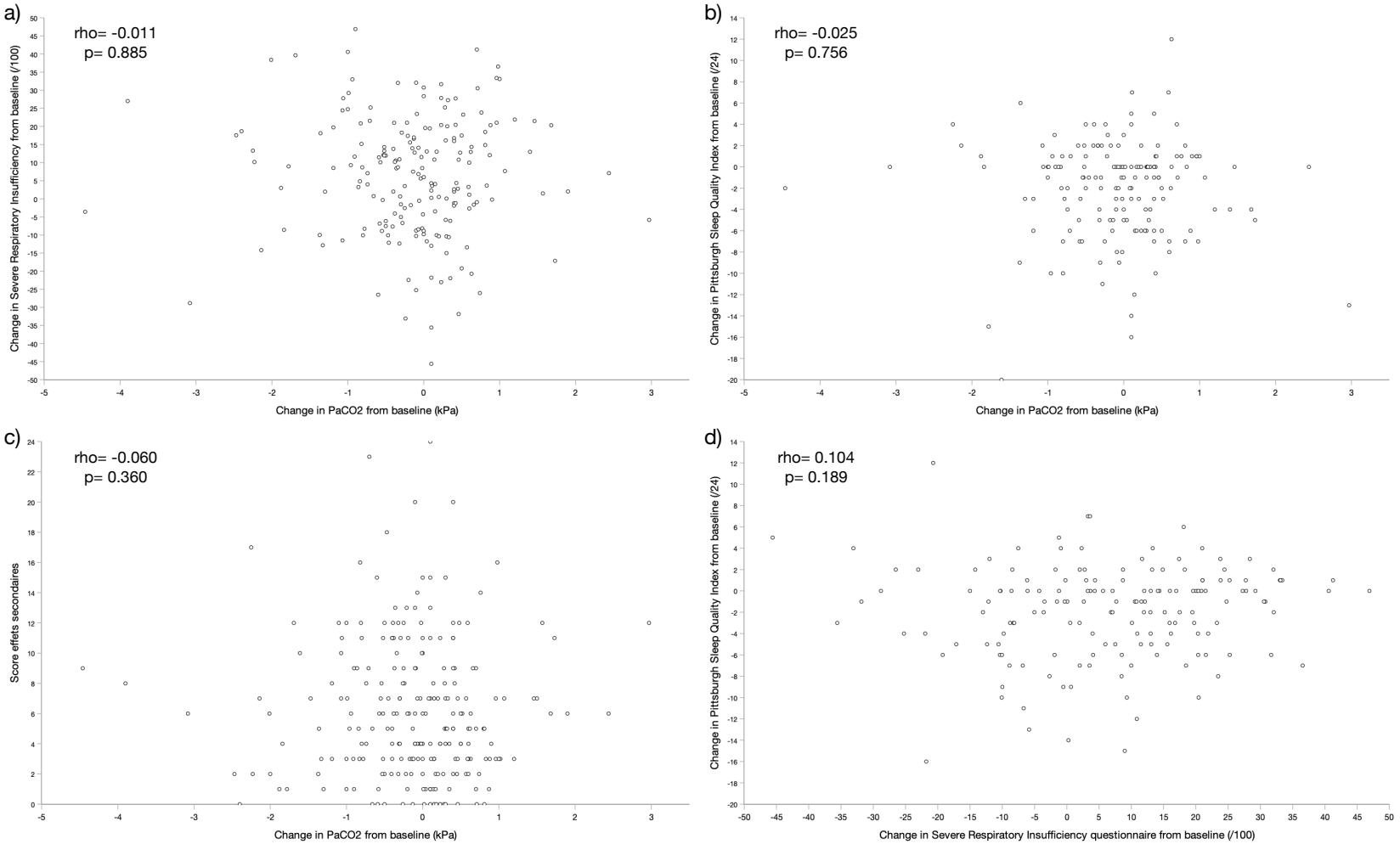
Out of the five goals assessed at follow-up, we found only a correlation between NIV adherence and change in PaCO2 (rho= -0.149, p=0.031). None of the other outcome were correlated (eFigure 2 and 3).

Correlation between the PSQI and the SRI specific sleep domain

The SRI is a multidimensional scale that includes a specific sleep domain. At baseline, we found no correlation between this subdomain and the PSQI (rho= -0,102; p=0,116). At follow-up, we found a significant correlation between the SRI sleep domain and the follow-up PSQI: (rho= -0,359; p<0.001).



eFigure 2: Correlation between daily compliance since NIV initiation and a) change in PaCO2 b) change in quality of life assessed by the Severe Respiratory insufficiency questionnaire c) change in sleep quality assessed by the Pittsburgh Sleep Quality Index and d) Side effects secondary to NIV use (sum of the severity grade of each side effect (maximum /48).



eFigure 3: Correlation between the change in PaCO2 since NIV initiation and a) change in quality of life assessed by the Severe Respiratory insufficiency questionnaire b) change in sleep quality assessed by the Pittsburgh Sleep Quality Index and c) Side effects secondary to NIV use (sum of the severity grade of each side effect (maximum /48). d) correlation between change in the Severe Respiratory insufficiency questionnaire and in the Pittsburgh Sleep Quality Index.

		Adherence ≥ 4h/day			Improvement in PaCO2			Improvement in SRI			Improvement in PSQI			Satisfactory tolerance		
		No	**Yes**	p	**No**	**Yes**	p	**No**	**Yes**	p	**No**	**Yes**	p	**No**	**Yes**	p
Adherence ≥ 4h/day	**No**	69 (100 %)	0 (0 %)	na												
	Yes	0 (0 %)	152 (100 %)													
Improvement in PaCO2	**No**	20 (44 %)	26 (57 %)	0.035	56 (100 %)	0 (0 %)	na									
	Yes	45 (27 %)	120 (73 %)		0 (0 %)	185 (100 %)										
Improvement in SRI	**No**	21 (29 %)	51 (71 %)	0.816	17 (22 %)	62 (79 %)	0.185	81 (100 %)	0 (0 %)	na						
	Yes	34 (32 %)	73 (68 %)		27 (24 %)	84 (76 %)		0 (0 %)	117 (100 %)							
Improvement in PSQI	**No**	28 (31 %)	62 (69 %)	0.711	23 (24 %)	75 (77 %)	0.917	35 (35 %)	64 (65 %)	0.706	100 (100 %)	0 (0 %)	na			
	Yes	17 (29 %)	41 (71 %)		15 (24 %)	47 (76 %)		28 (46 %)	33 (54 %)		0 (0 %)	63 (100 %)				
Satisfactory tolerance	**No**	29 (29 %)	71 (71 %)	0.765	32 (29 %)	78 (71 %)	0.021	37 (44 %)	47 (56 %)	0.440	50 (69 %)	23 (32 %)	0.121	113 (100 %)	0 (0 %)	na
	Yes	37 (31 %)	81 (69 %)		20 (16 %)	102 (84 %)		42 (39 %)	67 (62 %)		48 (57 %)	37 (44 %)		0 (0 %)	129 (100 %)	

eTable 3: Contingency table of goals achieved following NIV initiation.

Discussion:

In our cohort, patients with OHS had a significantly higher level of leaks than other diagnostic groups. We believe that this difference is related to the fact that patients with OHS had higher inspiratory and expiratory pressure than the others. As there was no difference in the level of leaks during the inpatient stay, this result stress the importance of finding the right balance between the level of pressure and leaks. It also highlights the fact that NIV delivery in the home setting differs from the hospital environment.

In our cohort, in univariate analysis, we have identified that patients adequate NIV setup was less likely to occur in patient with a more severe disease (worst dyspnea, daytime PaCO2 and overnight TcCO2). This group of patients may have had a more advanced respiratory disease. This result suggests that patients with more severe disease should have dedicated pathway for NIV setup. Our univariate analysis also shown that women were less likely to have adequate NIV setup. We were unable to identify why such difference was seen. Hypothesis to explain this difference could be a difference in symptoms perceptions, the fact that ventilators and specifically masks were designed for a predominantly male population or that women in our cohort had a more severe disease.

In our study, we found that the minimal detectable change in the SRI summary scale was +3.4 points. We used this difference to define a significant improvement in the HRQL in our study population. This cut-off is lower than the MCID reported recently (1). However, in that study, the MCID was only defined for COPD patients. In our cohort, the improvement in HRQL was lower than other published cohorts (2,3). However, like ABG assessment, our follow-up evaluation was conducted 9 weeks following NIV setup and HRQL may continue to improve during follow-up.

References:

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