Online data supplementary file

TITLE: Nocturnal noninvasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study

Acronym: RESCUE REspiratory Support in COPD after acUte Exacerbation.

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METHODS

Patients

Exclusion criteria were: 1) age < 18 or => 80 years; 2) significant bronchiectasis with recurrent infections; 3) significant heart failure; 4) kyphoscoliosis; 5) neuromuscular disease; 6) obstructive sleep apnea (Apnea Hypopnea Index: AHI >15 /hr); 7) current use of Continuous Positive Airway Pressure (CPAP) or Bi-level Positive Airway Pressure (BiPAP); 8) insufficient motivation for chronic ventilatory support; 9) social circumstances making chronic ventilatory support at home impossible; 10) other diagnoses limiting life expectations.

Home Mechanical Ventilation Center

In The Netherlands we have 4 legitimated and highly experienced Home Mechanical Ventilation Centers. Patients requiring chronic ventilation at home are sent in from all hospitals in the country to be established on mechanical ventilation by these centers. The nurse practitioners are allowed to establish long-term NIV also in external hospitals and deliver care at home. For this trial as a form of quality assurance, we set up a standardized protocol for establishment and NIV set up and organized a start up meeting to make sure everybody worked according to the same standard and regulations. Also, all centers worked with the same machines.

Intervention

Patients were instructed to use NIV during the night whilst asleep and, were advised to use NIV during the day/nap times if desired.

Measurements

An overnight polygraphy or Polysomnography was performed in patients with a body mass index ≥ 30 km/m^2, or in patients with complaints of excessive snoring, disrupted sleep or morning headache to exclude Obstructive Sleep Apnea Syndrome.

Survival, respiratory admission rates and days in hospital were checked in hospital registers and with patients general practitioner. Exacerbations at home were registered in a diary by the patient themselves.

An exacerbation was defined using a modified version of the definition of Rodriguez-Roisin, as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnoea, cough, and/or sputum that is beyond day-to-day variations, is acute in onset, and treated with antibiotics and/or prednisolone in patients with COPD.[1]

Lung function

Lung function measurements included routine spirometry by means of a pneumotachograph and according to ERS criteria.[2] Absolute values and % pred. according to normal values.

Transcutaneous measurement

Transcutaneous monitoring during the night was performed using the TOSCA[3] to measure skin-surface PO_2 and PCO_2 to provide estimates of arterial partial pressure of oxygen and carbon dioxide (PaO_2 and $PaCO_2$) and saturation. The device induces hyperperfusion by local heating of the skin of the earlobe and measures the partial pressure of oxygen and carbon dioxide electrochemically. The mean nocturnal $PtcCO_2$ was measured during the night before discharge out of hospital to see if patients were adequately adjusted to NIV. Patients in the standard treatment did not receive NIV during this measurement.

Health related quality of life questionnaires

Patients completed the following questionnaires concerning health related quality of life; the Clinical COPD Questionnaire (CCQ),[4] the Chronic Respiratory Questionnaire self reported (CRQ),[5] the Maugeri Respiratory Failure Questionnaire -28 (MRF-28)[6] and the Severe Respiratory Insufficiency (SRI) questionnaire.[7] The CCQ is a self-administered, 10-item questionnaire which can be divided into three domains: symptom, functional state and mental state. Scores range from 0 to 6 with high scores indicating extremely poor health status. The CRQ (self reported) contains 20 items and measures physical function and emotional function, divided into four domains: dyspnoea, fatigue, emotion and mastery. Scores range from 1 (worse) to 7 (best). The MRF-28 contains 28 items which are divided into 3 domains; daily activity, cognitive function and invalidity. The scores range from 0 (best) to 100 (worse). The SRI contains seven domains covering 49 items: respiratory complaints, physical functioning, attendant symptoms and sleep, social relationships, anxiety, psychological well-being and social functioning. Scoring ranges between 0-100, with high scores representing better HRQL.

Other measurements

The Groningen Activity and Restriction Scale (GARS) assesses activity and disability of daily living and consists of 18 items.[8] The Hospital Anxiety and Depression Scale (HADS) was used to determine levels of depression and anxiety.[9] It consists of 14 questions from which seven are on detection of anxiety and seven on depression (two subscales). Dyspnoea was measured using the Medical Research Council scale (MRC).[10]

We could not perform the 6-minute walking test since most patients were too weak to perform this test adequately and safely, raising ethical concerns. Our alternative of measuring walking distance with a pedometer also fell short, as we noticed that in the patients who

barely walk, shuffling occurs leading to an underestimation as the pedometer does not always detect their effort and thus real number of steps per day.

Statistical analysis

Continuous variables were summarized as means and standard deviations, or medians and ranges depending on their distribution. Changes within groups were compared using the paired sample T-test. Between group comparisons of continuous variables were performed using the independent samples T-test for variables with a normal distribution or the Mann-Whitney U test for variables with a non-normal distribution. Difference in change within groups and treatment effect between groups are shown as means with associated 95% confidence intervals (C.I.) and p-value ($p<0.05$ was considered statistically significant).

Supplementary file Table S1: Reasons for dropping out of study

	NIV n=25	Standard treatment n=24
Lack of motivation	15	14
Unable to come for testing	0	6
Discomfort associated with treatment	8	-
Critical intercurrent illness:		
- Dementia	1	0
- CVA	1	0
Switch to NIV	-	4

CVA cerebrovasculair accident; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.

Supplementary file Table S2: Causes of death

	ITT NIV n=30	ITT Standard treatment n=29	Non-drop outs NIV n=22	Non-drop outs Standard treatment n=22
Respiratory causes	21	25	15	20
Natural cause	3	3	3	1
Pneumothorax	1	1	1	1
Cardiac disease	3		1	
Lung carcinoma	1		1	
Missing	1		1	

ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.

Supplementary file Table S3: Changes in the Clinical COPD Questionnaire (CCQ) sub domains

	ITT Baseline	n	Completers Baseline	n	Completers 12 months		Change over 1 year	n
CCQ-Total								
NIV	3.4 ± 1.2	96	3.4 ± 1.2	48	2.9 ± 1.1	48	-0.5 (-0.2; -0.8) ¶	48
Controls	3.3 ± 1.2	90	3.2 ± 1.0	51	2.8 ± 1.1	51	-0.5 (-0.8; -0.1) ¶	51
Treatment effect							**-0.04 (-0.5; 0.4)**	
Symptom								
NIV	3.1 ± 1.2	99	3.0 ± 1.2	51	2.7 ± 1.2	51	-0.3 (-0.6; 0.1)	51
Controls	3.1 ± 1.1	90	3.2 ± 1.1	51	2.8 ± 1.1	51	-0.4 (-0.7; -0.04) ¶	51
Treatment effect							**-0.09 (-0.4; 0.6)**	
Functional								
NIV	4.1 ± 1.4	99	4.1 ± 1.5	49	3.5 ± 1.5	49	-0.5 (-0.9; -0.2) ¶	49
Controls	4.0 ± 1.4	90	3.9 ± 1.4	51	3.4 ± 1.4	51	-0.5 (-0.9; -0.1) ¶	51
Treatment effect							**-0.07 (-0.6; 0.5)**	
Mental								
NIV	2.6 ± 1.8	96	2.7 ± 1.8	50	1.7 ± 1.3	50	-1.0 (-1.4; -0.6) ¶	50
Controls	2.3 ± 1.7	90	2.2 ± 1.6	51	1.6 ± 1.5	51	-0.6 (-1.0; -0.2) ¶	51
Treatment effect							**-0.40 (-1.0; 0.2)**	

Data presented as means (± standard deviation) and mean change (95% confidence intervals).
CCQ, Clinical COPD Questionnaire; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.
¶ $p<0.05$ significant change after 12 months within the group.
*$p<0.05$ significant difference in change after 12 months between the groups (treatment effect).
Low CCQ scores indicate high quality of life. A negative treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.

Supplementary file Table S4: Changes in the Maugeri Respiratory Questionnaire-28 (MRF-28) sub domains

	ITT Baseline	n	Completers Baseline	n	Completers 12 months	n	Change over 1 year	n
MRF-28-Total								
NIV	60.9 ± 23.6	99	58.3 ± 24.3	50	51.0 ± 24.8	50	-7.3 (-12.5; -2.1) ¶	50
Controls	60.3 ± 23.9	90	55.3 ± 24.2	51	49.4 ± 25.0	51	-5.8 (-10.8; -0.8) ¶	51
Treatment effect							**-1.5 (-8.6; 5.7)**	
Daily activities								
NIV	62.3 ± 28.4	99	62.0 ± 29.9	50	54.5 ± 35.4	50	-7.5 (-15.09 ; 0.03)	50
Controls	61.7 ± 30.5	90	55.6 ± 30.7	51	46.3 ± 29.2	51	-9.3 (-16.1; -2.4) ¶	51
Treatment effect							**1.7 (-8.4; 11.8)**	
Cognition								
NIV	48.5 ± 41.0	99	44.5 ± 40.8	50	33.7 ± 36.3	50	-10.8 (-22.5; 0.8)	50
Controls	43.3 ± 35.9	90	39.7 ± 35.4	51	36.3 ± 35.5	51	-3.4 (-12.7; 5.8)	51
Treatment effect							**-7.4 (-22.0; 7.2)**	
Invalidity								
NIV	74.2 ± 31.2	99	70.6 ± 34.0	50	69.5 ± 34.8	50	-1.1 (-9.4; 7.2)	50
Controls	68.7 ± 33.5	90	59.2 ± 37.7	51	57.3 ± 39.4	51	-2.0 (-10.0; 6.1)	51
Treatment effect							**0.9 (-10.6; 12.3)**	

Data presented as means (± standard deviation) and mean change (95% confidence intervals).
ITT, intention-to-treat; MRF-28, Maugeri Respiratory Questionnaire-28; n, numbers for analysis;
NIV, noninvasive positive pressure ventilation.
¶ $p<0.05$ significant change after 12 months within the group.
*$p<0.05$ significant difference in change after 12 months between the groups (treatment effect).
Low MRF-28 scores indicate high quality of life. A negative treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.

Supplementary file Table S5: Changes in the Clinical Respiratory Questionnaire (CRQ) sub domains

	ITT Baseline	n	Completers Baseline	N	Completers 12 months	n	Change score 12 months	n
CRQ-Total								
NIV	3.5 ± 1.1	100	3.5 ± 1.1	50	4.2 ± 1.2	50	0.7 (0.4; 1.1) ¶	50
Controls	3.6 ± 1.1	89	3.6 ± 1.1	50	4.4 ± 1.2	50	0.7 (0.4; 1.0) ¶	50
Treatment effect							**0.01 (-0.4; 0.4)**	
Dyspnoea								
NIV	3.0 ± 2.7	100	3.1 ± 1.6	49	3.5 ± 1.7	49	0.4 (0.03; 0.8) ¶	49
Controls	3.25 ± 1.4	85	3.4 ± 1.5	46	3.9 ± 1.5	46	0.5 (-0.002; 0.9)	46
Treatment effect							**-0.02 (-0.6; 0.6)**	
Fatigue								
NIV	2.70 ±1.3	100	2.8 ± 1.3	50	3.8 ± 1.5	50	1.0 (0.5; 1.4) ¶	50
Controls	2.62 ±1.2	89	2.5 ± 1.0	50	3.7 ± 1.3	50	1.1 (0.8; 1.5) ¶	50
Treatment effect							**-0.2 (-0.7; 0.4)**	
Emotion								
NIV	3.93 ±1.3	100	3.9 ± 1.3		4.6 ± 1.3	50	0.7 (0.3; 1.1) ¶	50
Controls	4.09 ±1.2	89	4.1 ± 1.3	50	4.7 ± 1.4	50	0.6 (0.3; 0.9) ¶	50
Treatment effect							**0.1 (-0.4; 0.6)**	
Mastery								
NIV	3.86 ±1.4	100	3.8 ± 1.4	50	4.6 ± 1.4	50	0.8 (0.4; 1.2) ¶	50
Controls	4.01 ±1.4	89	4.0 ± 1.4	50	5.0 ± 1.4	50	0.9 (0.5; 1.3) ¶	50
Treatment effect							**-0.1 (-0.7; 0.4)**	

Data presented as means (± standard deviation) and mean change (95% confidence intervals).
CRQ, Clinical Respiratory Questionnaire; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation.
¶ $p<0.05$ significant change after 12 months within the group.
*$p<0.05$ significant difference in change after 12 months between the groups (treatment effect).
High CRQ scores indicate high quality of life. A positive treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.

Supplementary file Table S6: Changes in the Severe Respiratory Insufficiency questionnaire (SRI) sub domains

	ITT Baseline	n	Completers Baseline	N	Completers 12 months	n	Change score 12 months	n
SRI-Total								
NIV	48.1 ± 15.0	100	47.9 ± 15.1	50	55.0 ± 15.4	50	7.0 (3.4; 10.7) ¶	50
Controls	51.3 ± 15.9	90	53.6 ± 16.9	51	55.8 ± 16.3	51	2.2 (-1.2; 5.6)	51
Treatment effect							**4.8 (-0.1; 9.7)**	
Respiratory complaints								
NIV	47.9 ± 19.6	100	48.9 ± 21.2	50	55.6 ± 19.4	50	6.7 (2.1; 11.2) ¶	50
Controls	44.0 ± 18.6	90	45.7 ± 18.5	51	54.3 ± 16.7	51	8.6 (3.8; 13.5) ¶	51
Treatment effect							**-2.0 (-8.6; 4.6)**	
Physical functioning								
NIV	32.0 ± 18.5	100	32.7 ± 21.6	50	36.5 ± 21.6	50	3.8 (-1.4; 9.0)	50
Controls	32.5 ± 21.9	90	37.3 ± 21.4	51	41.3 ± 21.6	51	4.1 (-1.7; 9.9)	51
Treatment effect							**0.3 (-8.0; 7.4)**	
Attendant symp+sleep								
NIV	57.1 ± 18.4	100	54.4 ± 17.9	50	64.8 ± 18.0	50	10.4 (5.3; 15.5) ¶	50
Controls	58.6 ± 20.0	90	59.9 ± 22.3	51	61.7 ± 18.4	51	1.7 (-2.9; 6.4)	51
Treatment effect							**8.7 (1.9; 15.4)** *	
Social relationships								
NIV	58.3 ± 17.1	100	56.3 ± 14.0	50	60.9 ± 18.9	50	4.6 (-0.2; 9.4)	50
Controls	66.5 ± 17.1	90	68.2 ± 17.3	51	64.3 ± 17.4	51	-3.9 (-7.7; 0.03)	51
Treatment effect							**8.4 (2.4; 14.5)***	
Anxiety								
NIV	46.2 ± 22.5	100	47.0 ± 24.6	50	59.8 ± 22.1	52	12.8 (7.1; 18.5) ¶	50
Controls	50.4 ± 25.4	90	52.6 ± 26.3	51	58.2 ± 23.0	51	5.7 (0.6; 10.7) ¶	51
Treatment effect							**7.1 (-0.4; 14.6)**	
Well-being								
NIV	52.6 ± 20.1	100	52.2 ± 19.1	50	58.1 ± 22.9	50	5.9 (0.7; 11.1) ¶	50
Controls	59.3 ± 20.4	90	60.4 ± 22.1	51	60.3 ± 21.3	51	-0.1 (-4.7; 4.4)	51
Treatment effect							**6.0 (-0.8; 12.8)**	
Social functioning								
NIV	43.1 ± 40.6	100	44.0 ± 19.4	50	49.1 ±20.1	50	5.1 (-0.2; 10.4)	50
Controls	48.0 ± 20.4	90	51.4 ± 21.6	51	50.7 ± 23.1	51	-0.8 (-5.9; 4.4)	51
Treatment effect							**5.9 (-1.4; 13.2)**	

Data presented as means (± standard deviation) and mean change (95% confidence intervals). Attendant symp+sleep, attendant symptoms and sleep sub domain; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; SRI, Severe Respiratory Insufficiency questionnaire.

¶ $p<0.05$ significant change after 12 months within the group.

*$p<0.05$ significant difference in change after 12 months between the groups (treatment effect).

High SRI scores indicate high quality of life. A positive treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.

Supplementary file Table S7: Changes in the Groningen Activity and Restriction Scale (GARS), Hospital Anxiety and Depression Scale (HADS) and Medical Research Council (MRC) sub domains

	ITT Baseline	n	Completers Baseline	n	Completers 12 months	n	Change score 12 months	n
GARS-Total								
NIV	36.7 ± 7.5	100	36.3 ± 8.3	50	34.6 ± 9.4	50	-1.6 (-3.3; 0.1)	50
Controls	36.8 ± 8.5	90	34.7 ± 1.2	51	32.7 ± 8.2	51	-2.0 (-4.1; 0.1)	51
Treatment effect							**0.4 (-2.3; 3.0)**	
HADS-Total								
NIV	15.9 ± 9.2	98	15.6 ± 8.5	48	13.9 ± 8.8	48	-1.7 (-4.0; 0.6)	48
Controls	14.5 ± 8.8	87	13.1 ± 9.1	50	12.7 ± 9.3	50	-0.4 (-2.2; 1.3)	50
Treatment effect							**-1.3 (-4.1; 1.6)**	
HADS anxiety								
NIV	7.8 ± 5.0	99	7.9 ± 4.7	49	6.6 ± 4.7	49	-1.3 (-2.3; -0.2) ¶	49
Controls	7.3 ± 4.6	88	6.8 ± 4.8	51	5.9 ± 4.8	51	-0.9 (-1.8; 0.02)	51
Treatment effect							**-0.4 (-1.8; 1.0)**	
HADS depression								
NIV	8.1 ± 4.9	99	7.5 ± 4.8	50	7.1 ± 4.6	50	-0.4 (-1.7; 0.9)	50
Controls	7.1 ± 4.7	87	6.3 ± 4.7	50	6.7 ± 5.1	50	0.4 (-0.6; 1.5)	50
Treatment effect							**-0.8 (0.8; -2.5)**	
MRC								
NIV	3.9 ± 1.0	98	3.8 ± 1.4	49	3.5 ± 1.4	49	-0.4 (-0.7; -0.02) ¶	49
Controls	3.8 ± 1.0	90	3.6 ± 1.1	51	3.3 ± 1.2	51	-0.3 (-0.7; 0.08)	51
Treatment effect							**-0.05 (-0.6; 0.5)**	

Data presented as means (± standard deviation) and mean change (95% confidence intervals).
GARS, Groninger Activity Restriction Scale; HADS, Hospital Anxiety and Depression Scale; ITT, intention-to-treat; n, numbers for analysis; NIV, noninvasive positive pressure ventilation; MRC, Medical Research Council dyspnoea scale.

¶ $p<0.05$ significant change after 12 months within the group.

*$p<0.05$ significant difference in change after 12 months between the groups (treatment effect).

Low GARS scores indicate better daily activity levels. Low HADS scores indicate better mood state. Lower MRC scores represent less dyspnoea. A negative treatment effect signifies a bigger improvement after 12 months for the NIV group compared to standard treatment.

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