

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1. Comparison of Patients Who Met Criteria for Postextubation Respiratory Failure and for Reintubation According to Randomization Group**

	High-flow nasal oxygen alone (n=302)	High-flow nasal oxygen with NIV (n=339)	P value
<b>Post-extubation respiratory failure at day 7, No. (%)</b>	88 (29)	70 (21)	.02
- Respiratory rate > 25 breaths per minute, No. (%)	74 (24)	63 (19)	.07
- Clinical signs suggesting respiratory distress, No. (%)	57 (19)	46 (14)	.07
- Respiratory acidosis, No. (%)	21 (7)	18 (5)	.38
- Hypoxemia, No. (%)	52 (17)	36 (11)	.02
<b>Reintubation up until ICU discharge, No. (%)</b>	59 (20)	41 (12)	.009
<b>Criteria for reintubation</b>			
- Severe respiratory failure, No. (%)	46 (15)	42 (12)	.30
Respiratory rate > 35 breaths per minute, No. (%)	34 (11)	32 (9)	.45
Clinical signs suggesting respiratory distress, No. (%)	39 (13)	37 (11)	.43
Respiratory acidosis, No. (%)	12 (4)	9 (3)	.35
Hypoxemia, No. (%)	24 (8)	19 (6)	.24
- Hemodynamic failure, No. (%)	10 (3)	6 (2)	.21
- Neurological failure, No. (%)	18 (6)	19 (6)	.85
- Respiratory or cardiac arrest, No. (%)	7 (2)	3 (1)	.20
<b>Reasons for reintubation</b>			
Cardiogenic pulmonary edema, No. (%)	9 (3)	7 (2)	.46
Upper airway obstruction, No. (%)	6 (2)	6 (2)	.84
Aspiration, No. (%)	1 (0)	2 (1)	.99
Pneumonia, No. (%)	7 (2)	3 (1)	.14
Atelectasis, No. (%)	9 (3)	4 (1)	.11
Pleural effusion, No. (%)	2 (1)	3 (1)	.75
Pneumothorax, No. (%)	1 (0)	2 (1)	.99
Inability to clear secretions, No. (%)	18 (6)	18 (5)	.72
Ineffective cough, No. (%)	12 (4)	9 (3)	.35
Weakness of respiratory muscles, No. (%)	15 (5)	9 (3)	.12
Hypoventilation, No. (%)	0 (0)	2 (1)	.50
Hypercapnic coma, No. (%)	4 (1)	1 (0)	.14
Septic shock, No. (%)	4 (1)	1 (0)	.14
Cardiogenic shock, No. (%)	2 (1)	0 (0)	.22
Hemorrhage, No. (%)	3 (1)	0 (0)	.07
Neurologic event, No. (%)	7 (2)	7 (2)	.83
Surgery, No. (%)	3 (1)	1 (0)	.26

**eTable 2. Characteristics of the Patients According to PaCO<sub>2</sub> Level at Baseline**

	Non-hypercapnic patients (PaCO <sub>2</sub> ≤ 45 mm Hg)			Hypercapnic patients (PaCO <sub>2</sub> > 45 mm Hg)		
	High-flow nasal oxygen alone (n=254)	High-flow nasal oxygen with NIV (n=276)	P value	High-flow nasal oxygen alone (n=48)	High-flow nasal oxygen with NIV (n=63)	P value
<b>Characteristics of the patients at admission</b>						
Age, mean (SD), years	70 (10)	69 (10)	.3492	70 (9)	67 (11)	.1613
Male sex, No. (%)	167 (66)	190 (69)	.4481	28 (58)	40 (63)	.5805
Body-mass index, mean (SD), kg/m <sup>2</sup>	28 (6)	28 (7)	.8387	31 (7)	31 (9)	.8397
SAPS II at admission, mean (SD), points <sup>A</sup>	56 (18)	56 (20)	.9481	54 (16)	51 (19)	.4512
<b>Main reason for intubation, No. (%)</b>			.8290			--
Acute respiratory failure	123 (48)	126 (46)		35 (73)	41 (65)	
Coma	47 (19)	47 (17)		8 (17)	10 (16)	
Shock	27 (11)	33 (12)		3 (6)	4 (6)	
Cardiac arrest	24 (9)	34 (12)		2 (4)	1 (2)	
Surgery	28 (11)	28 (10)		0 (0)	7 (11)	
Other reason	5 (2)	8 (3)		0	0	
<b>Risk factors of extubation failure</b>						
Age > 65 years, No. (%)	188 (74)	199 (72)	.6199	35 (73)	38 (60)	.1658
Underlying chronic cardiac disease, No. (%) <sup>B</sup>	126 (50)	138 (50)	.9278	19 (40)	23 (37)	.7407
Ischemic heart disease, n	66	77		12	11	
Atrial fibrillation, n	50	35		8	10	
Left ventricular dysfunction, n	33	46		6	6	
History of cardiogenic pulmonary edema, n	17	20		4	5	
Underlying chronic lung disease, No. (%) <sup>B</sup>	54 (21)	80 (29)	0.0409	33 (69)	46 (73)	0.6230
Chronic obstructive pulmonary disease, n	42	55		22	31	
Obesity-hypoventilation syndrome, n	9	7		7	13	
Chronic restrictive pulmonary disease, n	7	21		5	3	
<b>Characteristics of the patients the day of extubation</b>						
SOFA score, mean (SD), points <sup>C</sup>	4.3 (2.7)	4.4 (2.6)	.4970	3.6 (1.6)	4.3 (3.1)	.1484
Duration of mechanical ventilation, median (IQR), days	5 (3–9)	6 (3–10)	.1319	6 (4–10)	5 (3–12)	.4787
Weaning difficulty No. (%) <sup>D</sup>			.5533			.3187
Simple weaning	177 (70)	194 (70)		26 (54)	38 (60)	
Difficult weaning	70 (27)	70 (25)		22 (46)	23 (37)	
Prolonged weaning	7 (3)	12 (5)		0 (0)	2 (3)	

	Non-hypercapnic patients (PaCO <sub>2</sub> ≤ 45 mm Hg)			Hypercapnic patients (PaCO <sub>2</sub> > 45 mm Hg)		
	High-flow nasal oxygen alone (n=254)	High-flow nasal oxygen with NIV (n=276)	P value	High-flow nasal oxygen alone (n=48)	High-flow nasal oxygen with NIV (n=63)	P value
<b>Ventilator settings before the spontaneous breathing trial</b>						
Assist-control ventilation, No. (%)	37 (15)	45 (16)	.5806	5 (10)	4 (6)	.4367
Pressure-support ventilation, No. (%)	217 (85)	231 (84)	.5806	43 (90)	59 (94)	.4367
Pressure-support level, mean (SD), cm H <sub>2</sub> O	9.4 (2.7)	9.2 (3.0)	.4147	10.4 (2.9)	9.9 (2.2)	.3163
PEEP, mean (SD), cm H <sub>2</sub> O	5.7 (1.6)	5.8 (1.5)	.1580	5.9 (1.7)	6.0 (1.9)	.7207
Tidal volume, mean (SD), ml	480 (125)	480 (143)	.9664	409 (110)	479 (147)	.009
Tidal volume, mean (SD), ml/kg	7.9 (2.4)	7.9 (2.5)	.9582	6.7 (1.6)	7.7 (2.3)	.0086
Respiratory rate, mean (SD), breaths/min	22 (7)	22 (6)	.7534	23 (6)	22 (7)	.4974
FiO <sub>2</sub> , mean (SD), %	34 (9)	35 (11)	.3846	38 (10)	37 (10)	.7881
PaO <sub>2</sub> :FiO <sub>2</sub> , mean (SD), mm Hg	281 (93)	281 (88)	.9926	236 (79)	247 (91)	.4927
pH, mean (SD), units	7.45 (0.06)	7.45 (0.05)	.6397	7.43 (0.05)	7.43 (0.05)	.9343
PaCO <sub>2</sub> , mean (SD), mm Hg	37 (6)	37 (8)	.3584	51 (7)	51 (8)	.6504
<b>Characteristics at the end of the spontaneous breathing trial</b>						
T-piece trial, No. (%)	161 (63)	172 (62)	.7996	27 (56)	34 (54)	.8108
Low level of pressure-support, No. (%)	93 (37)	104 (38)	.7996	21 (44)	29 (46)	.8108
Duration, median (IQR), min	60 (30-60)	60 (30-60)	.5452	60 (30-72)	60 (30-60)	.3719
Systolic arterial pressure, mean (SD), mm Hg	135 (21)	135 (23)	.7474	140 (20)	136 (21)	.3383
Diastolic arterial pressure, mean (SD), mm Hg	66 (14)	68 (16)	.4308	71 (13)	69 (16)	.4674
Heart rate, mean (SD), beats/min	92 (17)	91 (18)	.3496	90 (19)	96 (18)	.0903
Respiratory rate, mean (SD), breaths/min	23 (6)	23 (6)	.2576	24 (6)	23 (7)	.4892
SpO <sub>2</sub> , mean (SD), %	97 (3)	97 (3)	.7770	95 (3)	95 (3)	.9510
PaO <sub>2</sub> , mean (SD), mm Hg	89 (29)	87 (27)	.6288	75 (14)	81 (27)	.2201
pH, mean (SD), units	7.46 (0.06)	7.46 (0.05)	.4922	7.42 (0.04)	7.43 (0.05)	.5496
PaCO <sub>2</sub> , mm Hg	37 (5)	37 (5)	.9777	53 (7)	52 (9)	.4431
Steroids administration before extubation	35 (14)	38 (14)	.9970	7 (15)	15 (24)	.2270
Ineffective cough, No./total No. (%)	51/239 (21)	70/263 (27)	.1674	14/45 (69)	16/59 (73)	.6561
Abundant secretions, No./total No. (%)	101/242 (42)	91/265 (34)	.0864	20/46 (57)	23/61 (62)	.5465

**Abbreviations:** NIV = Non-invasive ventilation; SAPS = Simplified Acute Physiology Score; SOFA = Sepsis-related Organ Failure Assessment.

<sup>A</sup> The Simplified Acute Physiology Score (SAPS) II was calculated from 17 variables at admission. Scores range from 0 to 163, with higher scores indicating more severe disease and higher mortality risk.

<sup>B</sup> Patients could have more than one underlying chronic cardiac or lung disease.

<sup>C</sup> The Sepsis-related Organ Failure Assessment (SOFA) was calculated from 6 variables the day of extubation. Scores range from 0 to 24, with higher scores indicating more severe organ failure and higher mortality risk.

<sup>D</sup> Weaning difficulty was defined as following: simple weaning included patients extubated after success of the first spontaneous breathing trial, difficult weaning included patients who failed the first spontaneous breathing trial and were extubated within the 7 following days, and prolonged weaning included patients extubated more than 7 days after the first spontaneous breathing trial.

**eTable 3. Primary and Secondary Outcomes in Hypercapnic Patients (PaCO<sub>2</sub> > 45 mm Hg)**

	High-flow nasal oxygen alone (n=48)	High-flow nasal oxygen with NIV (n=63)	Absolute difference (95 CI)	P value
<b>Primary outcome</b>				
Reintubation at day 7, No. (%)	10 (21)	5 (8)	-12.9 (-27.1 to -0.1)	<b>.0489</b>
<b>Secondary outcomes</b>				
Post-extubation respiratory failure at day 7, No. (%)	24 (50)	14 (22)	-27.8 (-43.8 to -9.8)	<b>.0022</b>
Reintubation at 48 hours, No. (%)	4 (8)	2 (3)	-5.2 (-16.6 to 4.0)	.2337
Reintubation at 72 hours, No. (%)	9 (19)	4 (6)	-12.4 (-26.1 to -0.10)	<b>.0441</b>
Reintubation up until ICU discharge, No. (%)	10 (21)	6 (9)	-11.3 (-25.7 to 2.0)	.0928
Patient meeting reintubation criteria during ICU stay, No. (%)	11 (23)	7 (11)	-11.8 (-26.5 to 2.1)	.0946
Length of stay in ICU, median (IQR) days	13 (9–18)	13 (7–20)	0.6 (-4.0 to 5.2)	.7592
Length of stay in hospital, median (IQR) days	24 (15–29)	26 (15–36)	2.5 (-4.9 to 9.9)	.4234
Mortality in ICU, No. (%)	5 (10)	2 (3)	-7.2 (-19.2 to 2.4)	.1199
Mortality or reintubation in ICU, No. (%)	11 (23)	6 (9)	-13.4 (-27.9 to 0.3)	.0523
Mortality in ICU of reintubated patients, No. (%)	4/10 (40)	2/6 (33)	-6.7 (-43.9 to 36.7)	.9999
Mortality in hospital, No. (%)	7 (15)	8 (13)	-1.9 (-15.9 to 10.8)	.7735
Mortality at day 90, No. (%)	11 (23)	12 (19)	-3.9 (-19.6 to 11.0)	.6183

**Abbreviations:** NIV = Non-invasive ventilation; 95 CI = 95% confident interval; ICU = intensive care unit.

**eTable 4. Primary and Secondary Outcomes in Nonhypercapnic Patients (PaCO<sub>2</sub> ≤ 45 mm Hg)**

	High-flow nasal oxygen alone (n=254)	High-flow nasal oxygen with NIV (n=276)	Absolute difference (95 CI)	P value
<b>Primary outcome</b>				
Reintubation at day 7, No. (%)	45 (18)	35 (13)	-5.0 (-11.2 to 1.1)	.1057
<b>Secondary outcomes</b>				
Post-extubation respiratory failure at day 7, No. (%)	64 (25)	56 (20)	-4.9 (-12.0 to 2.2)	.1775
Reintubation at 48 hours, No. (%)	32 (13)	22 (8)	-4.6 (-10.0 to 0.6)	.0785
Reintubation at 72 hours, No. (%)	38 (15)	26 (9)	-5.5 (-11.2 to 0.0)	.0505
Reintubation up until ICU discharge	49 (19)	35 (13)	-6.6 (-12.9 to -0.4)	<b>.0374</b>
Patient meeting reintubation criteria during ICU stay, No. (%)	54 (21)	42 (15)	-6.0 (-12.6 to 0.5)	.0712
Length of stay in ICU, median (IQR), days	11 (7–19)	12 (7–18)	0.5 (-1.8 to 2.8)	.4087
Length of stay in hospital, median (IQR), days	23 (15–40)	25 (15–43)	2.0 (-2.2 to 6.2)	.4181
Mortality in ICU, No. (%)	21 (8)	19 (7)	-1.4 (-6.1 to 3.2)	.5548
Mortality or reintubation in ICU, No. (%)	53 (21)	45 (16)	-4.6 (-11.2 to 2.1)	.1766
Mortality in ICU of reintubated patients, No. (%)	17/49 (35)	9/35 (26)	-8.9 (-27.1 to 11.2)	.3801
Mortality in hospital, No. (%)	39 (15)	46 (17)	1.3 (-5.0 to 7.5)	.6808
Mortality at day 90, No. (%)	54 (21)	50 (18)	-3.8 (-9.9 to 3.6)	.3626

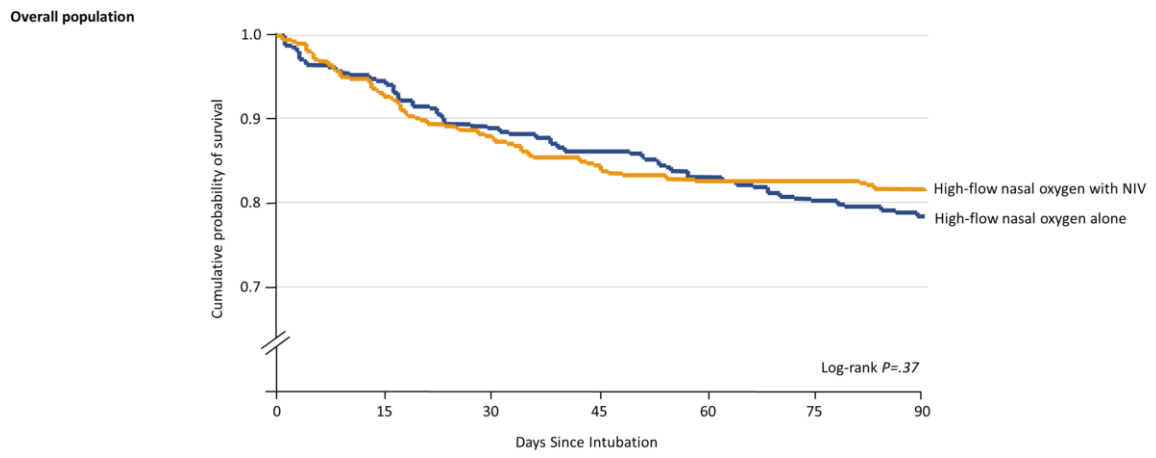
**Abbreviations:** NIV = Non-invasive ventilation; ICU = intensive care unit.

**eTable 5. Number of Patients Included per Center and Reintubation Rates per Center According to Randomization Group.**

	<b>Reintubation rates per center at day 7</b>	<b>Reintubation rates in the high-flow nasal oxygen alone group</b>	<b>Reintubation rates in the non-invasive ventilation group</b>
Center 1	1/38 (3%)	1/19 (5%)	0/19 (0%)
Center 2	3/32 (9%)	0/16 (0%)	3/16 (19%)
Center 3	1/14 (7%)	0/7 (0%)	1/7 (14%)
Center 4	5/32 (16%)	2/15 (13%)	3/17 (18%)
Center 5	7/13 (54%)	3/6 (50%)	4/7 (57%)
Center 6	4/27 (15%)	2/13 (15%)	2/14 (14%)
Center 7	6/23 (26%)	6/10 (60%)	0/13 (0%)
Center 8	3/12 (25%)	2/5 (40%)	1/7 (14%)
Center 9	7/34 (21%)	5/17 (29%)	2/17 (12%)
Center 10	2/22 (9%)	2/10 (20%)	0/12 (0%)
Center 11	5/24 (21%)	3/11 (27%)	2/13 (15%)
Center 12	0/3 (0%)	0/1 (0%)	0/2 (0%)
Center 13	5/25 (20%)	3/12 (25%)	2/13 (15%)
Center 14	8/24 (33%)	6/11 (55%)	2/13 (15%)
Center 15	3/24 (13%)	2/12 (17%)	1/12 (8%)
Center 16	4/23 (17%)	1/10 (10%)	3/13 (23%)
Center 17	4/25 (16%)	1/12 (8%)	3/13 (23%)
Center 18	1/7 (14%)	1/2 (50%)	0/5 (0%)
Center 19	0/11 (0%)	0/5 (0%)	0/6 (0%)
Center 20	5/48 (10%)	3/25 (12%)	2/23 (9%)
Center 21	4/17 (24%)	1/8 (13%)	3/9 (33%)
Center 22	1/6 (17%)	1/2 (50%)	0/4 (0%)
Center 23	3/40 (8%)	2/19 (11%)	1/21 (5%)
Center 24	1/31 (3%)	1/14 (7%)	0/17 (0%)
Center 25	0/6 (0%)	0/3 (0%)	0/3 (0%)
Center 26	2/21 (10%)	2/10 (20%)	0/11 (0%)
Center 27	2/9 (22%)	1/4 (25%)	1/5 (20%)
Center 28	4/30 (13%)	3/14 (21%)	1/16 (6%)
Center 29	1/4 (25%)	0/2 (0%)	1/2 (50%)
Center 30	3/16 (19%)	1/7 (14%)	2/9 (22%)
<b>Total</b>	<b>95/641 (15%)</b>	<b>55/302 (18%)</b>	<b>40/339 (12%)</b>



**eFigure. Kaplan-Meier Curves of the Cumulative Probability of Survival From Extubation to Day 90.**



Number at risk

High-flow nasal oxygen alone	302	284	268	260	251	242	237
High-flow nasal oxygen with NIV	339	314	298	286	280	280	277