

## Prophylactic Surfactant Nebulization for the Early Aeration of the Preterm Lung –

### A Randomized Clinical Trial

### Supplementary Information

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## Supplementary Methods

### Respiratory failure criteria

Failure of noninvasive respiratory support *in the delivery room* is defined by the presence of at least one of the following criteria:

- Bradycardia (<100 beats per minute) for  $\geq 30$  seconds despite NIPPV support
- No (adequate) air entry despite the use of non-invasive ventilation
- No breathing efforts after 3-5 minutes of NIPPV
- $FiO_2 > 0.4$  while on CPAP to reach preductal  $SpO_2$  values  $\geq 90\%$

During the first 24 hours of life, *failure of noninvasive respiratory support in the NICU* is defined by the presence of at least one of the following criteria:

- Sustained increase in  $FiO_2 > 0.4$  to keep  $SpO_2$  between 87-95%
- $> 3$  apneas requiring stimulation per hour
- Respiratory acidosis with a  $pH < 7.1$

If respiratory failure is due to insufficient oxygenation, infants  $\geq 28$  weeks gestation at birth first receive minimally invasive surfactant application (MIST), while infants  $< 28$  weeks gestation are primarily intubated.

### EIT data collection

A researcher not otherwise involved in resuscitation was present for each delivery to set up data collection devices before birth: A textile EIT belt was fastened at nipple level as soon as the infant reached the resuscitaire. The LuMon<sup>TM</sup> device (SenTec AG, Landquart, Switzerland) was used to record EIT data at a frame rate of 51 Hz. The EIT belt remained on the infant's

thorax for the initial 90 minutes or until the first chest X-ray was performed and was re-applied at nipple level at 6, 12 and 24 hours after birth. At pre-defined timepoints (every ten minutes from 10 to 90 minutes as well as 6, 12 and 24 hours after birth), 30 seconds with artefact-free tidal ventilation were identified and data were extracted using ibeX (version 1.1, SenTec AG, Landquart, Switzerland). Recordings were excluded from analysis if the infant had received (additional) intratracheal surfactant, either via MIST or via intubation. Infants were lying in supine position during all measurements. Thus, dorsal lung regions were considered gravity-dependent.[1,2] EIT data were analyzed using Matlab software (version 2019a, Mathworks, Nantick, MA, USA) and all parameters were assessed over all timepoints.

### EIT data preparation

First, data was prepared by projecting predefined anatomical lung regions based on the vendor-provided human model chest atlas into the EIT image, excluding EIT signals outside of these regions and normalizing the signal for body weight.[1–3]

Second, the net EIT signal at end-expiration (end-expiratory lung impedance; EELI) was isolated in arbitrary units (AU) to assess overall lung aeration. This was determined in four horizontal quantiles ranging from non-gravity-dependent to gravity-dependent ( $EELI_{NGD}$ ,  $EELI_{midNGD}$ ,  $EELI_{midGD}$ ,  $EELI_{GD}$ ) to assess regional aeration.[2] Finally, aeration homogeneity ratio ( $AHR$ ) and outer  $AHR$  ( $AHR_{outer}$ ) were calculated in both groups.[2] To calculate  $AHR$ s, signals in each quantile of regional aeration were first weighted to the known pixel contribution of each region to normalize for differences in lung size,[2,4] and then the non-gravity-dependent half of the EIT signal was divided by the gravity-dependent half (for  $AHR$ ) or the outermost non-gravity-dependent quantile was divided by the most gravity-dependent quantile (for  $AHR_{outer}$ ).[2] For both ratios, a value of 1 represents equal distribution of air and

a value  $<1$  or  $>1$  describes an aeration which favours the gravity-dependent or non-gravity-dependent lung, respectively.

Third, overall changes in ventilation including tidal volumes ( $V_T$ ), inspiratory to expiratory ratio, silent spaces (SS), the deviation from the ideal centre of ventilation (ideal minus actual centre of ventilation;  $CoV_{i-a}$ ) and the coefficient of variation (CV) were calculated at each of the pre-defined timepoints and compared between the two groups.[2,5] Silent spaces correspond to areas of the lung with little or no ventilation,[6] and were calculated in the gravity-dependent (GD) and non-gravity-dependent (NGD) hemithorax separately ( $SS_{GD}$  and  $SS_{NGD}$ , respectively). The  $CoV_{i-a}$  is an indicator of global ventilation distribution (e.g. gravity-dependent vs gravity-non-dependent and right vs left). SS and  $CoV_{i-a}$  are percentages and thus, they were not normalized for body weight. Finally, the standard deviation (SD) of impedance changes in all pixels was divided by the mean value of impedance to calculate the coefficient of variation (CV).[2,7] The CV correlates with ventilation homogeneity and lower values indicate improved homogeneity.

## SUPPLEMENTARY TABLES

Variable	Surfactant nebulization (N=16)	Standard care (N=16)	p-value	P <sub>adj</sub>
<i>A) ΔEELI over time [AU/kg]</i>				
10 min	29 (23 – 54)	25 (14 – 37)	0.36	0.39
20 min	28 (11 – 67)	21 (10 – 32)	0.49	0.49
30 min	25 (7 – 62)	10 (0 – 26)	0.21	0.33
40 min	23 (2 – 49)	10 (0 – 18)	0.28	0.36
50 min	26 (-1 – 49)	7 (-12 – 25)	0.22	0.33
60 min	15 (-9 – 55)	6 (-11 – 11)	0.30	0.36
70 min	28 (0 – 55)	4 (-16 – 15)	0.09	0.24
80 min	34 (8 – 60)	4 (-8 – 16)	0.10	0.24
90 min	35 (30 – 63)	1 (-3 – 6)	0.19	0.33
6 hrs	73 (22 – 111)	28 (-4 – 44)	<b>0.04</b>	0.24
12 hrs	93 (83 – 137)	39 (15 – 78)	<b>0.009</b>	0.108
24 hrs	86 (50 – 123)	45 (21 – 77)	0.08	0.24
<i>B) Mean airway pressure over time [mbar]</i>				
10 min	10.8 (8.0 – 12.2)	8.0 (8.0 – 12.0)	0.56	0.83
20 min	9.1 (8.0 – 11.6)	8.0 (7.8 – 8.5)	0.14	0.83
30 min	8.0 (8.0 – 8.0)	8.0 (7.8 – 8.0)	0.37	0.83
40 min	8.0 (8.0 – 8.0)	7.5 (7.0 – 8.0)	0.23	0.83
50 min	8.0 (8.0 – 8.0)	7.5 (7.0 – 8.3)	0.28	0.83
60 min	8.0 (7.5 – 8.7)	7.0 (7.0 – 8.0)	0.19	0.83
70 min	8.0 (7.0 – 8.0)	7.0 (7.0 – 8.0)	0.69	0.83
80 min	8.0 (7.0 – 8.0)	7.0 (7.0 – 8.0)	0.56	0.83
90 min	8.0 (7.0 – 8.0)	7.0 (7.0 – 8.0)	0.57	0.83
6 hrs	6.5 (6.0 – 7.3)	7.0 (6.0 – 7.0)	0.98	0.98
12 hrs	6.0 (5.5 – 6.0)	6.0 (5.5 – 7.0)	0.83	0.91
24 hrs	5.0 (5.0 – 6.0)	6.0 (5.0 – 6.0)	0.67	0.83
<i>C) SpO<sub>2</sub>/FiO<sub>2</sub>-ratio over time</i>				
10 min	259 (171 – 345)	341 (260 – 396)	0.05	0.30
20 min	300 (240 – 342)	378 (339 – 410)	<b>0.04</b>	0.30
30 min	382 (302 – 432)	392 (324 – 431)	0.66	0.88
40 min	390 (355 – 448)	430 (344 – 457)	0.51	0.88
50 min	438 (317 – 455)	420 (347 – 463)	0.66	0.88
60 min	433 (305 – 455)	432 (351 – 458)	0.58	0.88
70 min	422 (335 – 461)	438 (340 – 462)	0.85	0.92
80 min	433 (372 – 466)	434 (334 – 457)	0.66	0.88
90 min	452 (351 – 457)	426 (372 – 467)	0.87	0.92
6 hrs	453 (423 – 462)	428 (398 – 450)	0.19	0.76

12 hrs	457 (386 – 467)	448 (427 – 462)	0.92	0.92
24 hrs	462 (387 – 467)	448 (417 – 462)	0.54	0.88
<b>D) Heart rate over time [bpm]</b>				
10 min	145 (140 – 163)	143 (140 – 155)	0.69	0.73
20 min	158 (153 – 179)	159 (150 – 169)	0.57	0.73
30 min	171 (153 – 177)	160 (157 – 173)	0.73	0.73
40 min	167 (155 – 173)	156 (148 – 171)	0.24	0.73
50 min	163 (152 – 170)	152 (150 – 165)	0.28	0.73
60 min	158 (148 – 169)	149 (145 – 161)	0.43	0.73
70 min	154 (151 – 167)	149 (142 – 159)	0.16	0.73
80 min	158 (149 – 162)	152 (141 – 162)	0.47	0.73
90 min	154 (148 – 162)	150 (142 – 160)	0.37	0.73
6 hrs	150 (136 – 156)	147 (142 – 153)	0.64	0.73
12 hrs	147 (137 – 154)	147 (135 – 150)	0.66	0.73
24 hrs	142 (137 – 155)	144 (139 – 158)	0.58	0.73

**Supplementary Table S1. Changes in end-expiratory lung impedance (A), mean airway pressure (B), SpO<sub>2</sub>/FiO<sub>2</sub>-ratio (C) and heart rate (D) over time.** Analysis for each timepoint is based only on infants who are non-invasively ventilated at the respective timepoint (see Figure 2 for exact numbers). NB: set mean airway pressure is shown. *Abbreviations:*  $p_{adj}$  = adjusted p-value using the Bonferroni-Holm method;  $\Delta$ EELI = changes in end-expiratory lung impedance, SpO<sub>2</sub> = peripheral oxygen saturation, FiO<sub>2</sub> = fraction of inspired oxygen.

Variable	Surfactant nebulization (N=16)	Standard care (N=16)	p-value	P <sub>adj</sub>
<i>A) ΔEELI non-gravity-dependent [AU/kg]</i>				
10 min	1.7 (0.5 to 2.56)	2.11 (0.43 to 4.06)	0.67	0.95
20 min	2.49 (0.51 to 5.13)	1.58 (0.21 to 4.08)	0.49	0.88
30 min	1.35 (0.38 to 4.1)	0.42 (-0.4 to 2.3)	0.30	0.85
40 min	0.49 (-0.28 to 3.03)	0.82 (-0.44 to 1.99)	0.92	1
50 min	3.12 (0.01 to 4.12)	0.88 (-0.63 to 3.41)	0.49	0.88
60 min	1.77 (-0.33 to 4.76)	0.39 (-1.38 to 3.34)	0.42	0.85
70 min	2.25 (1 to 4.42)	1.16 (0.15 to 3.24)	0.42	0.85
80 min	2.23 (1.02 to 3.81)	1.24 (-1.31 to 2.22)	0.29	0.85
90 min	1.79 (0.72 to 3.27)	0.03 (-0.8 to 2.08)	0.56	0.94
6 hrs	1.27 (-0.15 to 6)	2.04 (0.1 to 3.2)	0.98	1
12 hrs	5.93 (2.75 to 11.27)	2.75 (1.3 to 4.6)	0.10	0.61
24 hrs	3.92 (0.49 to 13.23)	3.43 (-0.82 to 3.78)	0.30	0.85
<i>B) ΔEELI mid-non-gravity-dependent [AU/kg]</i>				
10 min	8.27 (4.32 to 12.99)	9.73 (0.62 to 13.81)	0.99	1
20 min	7.04 (-1.2 to 22.61)	5.31 (1.59 to 10.95)	0.64	0.95
30 min	4.25 (-6.96 to 13.31)	5.31 (-1.71 to 10.11)	0.93	1
40 min	7.73 (-0.29 to 11.17)	2.58 (-2.68 to 6.11)	0.36	0.85
50 min	7.45 (-8.13 to 18.73)	2.65 (-3.05 to 9.93)	0.49	0.88
60 min	3.93 (-2.01 to 16.46)	1.24 (-8.57 to 7.15)	0.20	0.84
70 min	9.46 (0.26 to 21.12)	2.62 (-6.96 to 6.91)	0.14	0.70
80 min	12.06 (4.33 to 23.97)	2.78 (-4.74 to 8.19)	0.10	0.61
90 min	17.03 (7.73 to 21.36)	1.04 (-0.65 to 5.47)	0.29	0.85
6 hrs	25.03 (7.08 to 43.78)	7.73 (-14.76 to 20.35)	0.08	0.58
12 hrs	31.24 (25.08 to 56.1)	10.4 (-2.83 to 25.07)	<b>0.02</b>	0.41
24 hrs	32.17 (10.85 to 47.12)	21.44 (12.36 to 23.1)	0.12	0.64
<i>C) ΔEELI mid-gravity-dependent [AU/kg]</i>				
10 min	16.24 (10.76 to 22.24)	16.86 (4.3 to 26.04)	0.87	1
20 min	25.63 (10.99 to 32.22)	16.5 (6.85 to 23.67)	0.24	0.85
30 min	12.75 (-2.27 to 31.83)	14.38 (-0.42 to 21.01)	0.42	0.85
40 min	9.66 (-3.32 to 22.08)	7.85 (0.26 to 12.78)	0.49	0.88
50 min	11.72 (-5.07 to 26.85)	6.97 (-9.1 to 13.19)	0.36	0.85
60 min	3.55 (-8.12 to 16.94)	2.97 (-6.06 to 13.32)	0.68	0.95
70 min	10.98 (0.67 to 18.64)	3.2 (-15.17 to 12.4)	0.23	0.85
80 min	13.24 (4.68 to 25.29)	2.73 (-17.07 to 13.62)	0.18	0.77
90 min	24.38 (-3.28 to 41.52)	5.3 (-11.74 to 7.69)	0.41	0.85
6 hrs	57.11 (30.91 to 77.39)	16.63 (-1.92 to 27.26)	<b>0.003</b>	0.39
12 hrs	62.3 (50.17 to 93.01)	25.14 (4.11 to 45.65)	<b>0.008</b>	0.39

24 hrs	53.43 (32.19 to 73.34)	26.03 (-1.41 to 53.6)	0.13	0.69
<i>D) <math>\Delta</math>EELI gravity-dependent [AU/kg]</i>				
10 min	0.71 (-0.45 to 1.44)	0.85 (-0.5 to 1.71)	0.75	0.98
20 min	0.9 (0.26 to 1.49)	0.85 (0.04 to 1.63)	0.81	1
30 min	0.7 (0.06 to 1.7)	0.6 (-0.16 to 1.37)	0.64	0.95
40 min	0.54 (-1.68 to 0.91)	0.67 (-0.31 to 1.06)	0.68	0.95
50 min	0.5 (-0.2 to 1.19)	0.57 (-0.42 to 0.9)	0.68	0.95
60 min	-0.57 (-1.08 to 0.47)	0.2 (-0.98 to 0.95)	0.71	0.97
70 min	-0.2 (-0.56 to 1.12)	0.23 (-0.2 to 0.57)	0.97	1
80 min	0.81 (-0.69 to 1.22)	-0.17 (-0.37 to 0.97)	0.93	1
90 min	1.94 (-1.21 to 2.19)	0.22 (-1.65 to 0.35)	0.41	0.85
6 hrs	3.18 (1.53 to 5.15)	0.58 (-1.32 to 1.63)	<b>0.005</b>	0.39
12 hrs	4.03 (2.39 to 5.47)	1.91 (0.51 to 2.91)	<b>0.027</b>	0.41
24 hrs	3.27 (1.94 to 4.71)	1.52 (0.21 to 4.19)	0.17	0.76
<i>E) Aeration Homogeneity Ratio</i>				
10 min	0.68 (0.57 to 0.84)	0.69 (0.6 to 0.87)	0.72	0.97
20 min	0.69 (0.56 to 0.85)	0.68 (0.59 to 0.88)	0.72	0.97
30 min	0.69 (0.57 to 0.85)	0.7 (0.59 to 0.86)	0.75	0.98
40 min	0.63 (0.57 to 0.83)	0.7 (0.59 to 0.88)	0.60	0.95
50 min	0.63 (0.58 to 0.85)	0.71 (0.59 to 0.89)	0.60	0.95
60 min	0.63 (0.58 to 0.85)	0.69 (0.59 to 0.88)	0.65	0.95
70 min	0.7 (0.58 to 0.85)	0.69 (0.59 to 0.96)	0.63	0.95
80 min	0.62 (0.54 to 0.86)	0.68 (0.59 to 0.83)	0.66	0.95
90 min	0.8 (0.62 to 0.88)	0.61 (0.54 to 0.76)	0.73	0.97
6 hrs	0.72 (0.58 to 0.82)	0.71 (0.58 to 0.86)	0.77	0.99
12 hrs	0.79 (0.53 to 0.86)	0.71 (0.59 to 0.76)	0.84	1
24 hrs	0.82 (0.56 to 0.85)	0.68 (0.57 to 0.79)	0.95	1

**Supplementary Table S2. Changes in end-expiratory lung impedance across 4 horizontal slices (A-D) and Aeration Homogeneity Ratio (E) over time.** Analysis for each timepoint is based only on infants who are non-invasively ventilated at the respective timepoint (see Figure 2 for exact numbers). *Abbreviations:*  $\Delta$ EELI = changes in end-expiratory lung impedance,  $p_{adj}$  = adjusted p-value using the Bonferroni-Holm method.



Variable	Surfactant nebulization (N=16)	Standard care (N=16)	p-value	P <sub>adj</sub>
<i>A) Deviation from the ideal center of ventilation (right to left) [%]</i>				
10 min	5.27 (-1.86 to 7.53)	5.54 (-0.42 to 8.2)	0.93	1
20 min	6.05 (-1.04 to 8.12)	4.19 (0.03 to 9.97)	0.81	1
30 min	3.71 (-1.29 to 7.34)	9.17 (6.3 to 11.83)	<b>0.019</b>	0.411
40 min	6.36 (-0.75 to 7.53)	8.52 (6.94 to 10.65)	<b>0.024</b>	0.411
50 min	4.92 (-6.53 to 9.06)	8.41 (6.1 to 9.77)	0.078	0.582
60 min	4.23 (-5.04 to 10.02)	10.23 (7.24 to 12.08)	<b>0.049</b>	0.57
70 min	2.17 (0.33 to 5.44)	9.77 (7.06 to 11.13)	<b>0.021</b>	0.411
80 min	3.54 (1.02 to 5.11)	8.65 (1.59 to 11.76)	0.29	0.8504
90 min	3.51 (3.36 to 9.11)	4.32 (-8.38 to 12.25)	0.90	1
6 hrs	5.02 (0.75 to 10.81)	5.71 (-0.21 to 10.43)	0.95	1
12 hrs	4.23 (2.26 to 7.6)	4.13 (-2.19 to 7.29)	0.47	0.883
24 hrs	5.16 (-2.52 to 6.69)	8.09 (3.67 to 10.76)	0.30	0.8504
<i>B) Deviation from the ideal center of ventilation (ventral to dorsal) [%]</i>				
10 min	-3.11 (-3.86 to -0.33)	-3.04 (-5.49 to -2.06)	0.49	0.88
20 min	-2.46 (-6.31 to 0.77)	-4.75 (-6.02 to -1.76)	0.34	0.85
30 min	-2.33 (-5.41 to -0.31)	-1.66 (-4.05 to -0.37)	0.78	1
40 min	-3.94 (-7.22 to -1.68)	-1.73 (-3.17 to 0.47)	0.07	0.58
50 min	-3.86 (-7.18 to -1.25)	-1.1 (-2.4 to -0.48)	0.10	0.61
60 min	-4.24 (-6.56 to -1.5)	-2.22 (-5.39 to -0.58)	0.34	0.85
70 min	-4.23 (-7.97 to -2.87)	-2.07 (-2.42 to 0.33)	<b>0.043</b>	0.53
80 min	-5.57 (-7.54 to -3.72)	-1.92 (-4.48 to -1.79)	0.09	0.58
90 min	-7.49 (-7.62 to -5.12)	-2.49 (-3.93 to -1.29)	0.06	0.58
6 hrs	-5.86 (-8.92 to -4)	-5.37 (-6.54 to -3.37)	0.42	0.85
12 hrs	-4.39 (-8.8 to -2.91)	-4.49 (-5.3 to -2.04)	0.68	0.95
24 hrs	-5.28 (-6.54 to -4)	-3.1 (-4.22 to -2.35)	<b>0.035</b>	0.48
<i>C) Coefficient of variation</i>				
10 min	0.85 (0.67 to 1)	0.76 (0.66 to 0.89)	0.49	0.88
20 min	0.82 (0.74 to 1.08)	0.79 (0.64 to 1.03)	0.64	0.95
30 min	0.82 (0.59 to 1.04)	0.74 (0.68 to 0.85)	0.64	0.95
40 min	0.78 (0.64 to 1)	0.69 (0.64 to 0.76)	0.30	0.85
50 min	0.72 (0.6 to 1.03)	0.73 (0.61 to 0.88)	0.68	0.95
60 min	0.75 (0.64 to 0.86)	0.71 (0.61 to 0.77)	0.30	0.85
70 min	0.83 (0.66 to 0.96)	0.7 (0.6 to 0.91)	0.58	0.95
80 min	0.76 (0.61 to 0.92)	0.7 (0.64 to 0.85)	0.86	1
90 min	0.7 (0.69 to 0.72)	0.69 (0.56 to 0.97)	0.90	1
6 hrs	0.7 (0.61 to 0.81)	0.63 (0.61 to 0.75)	0.51	0.89
12 hrs	0.68 (0.67 to 0.73)	0.64 (0.56 to 0.69)	0.08	0.58

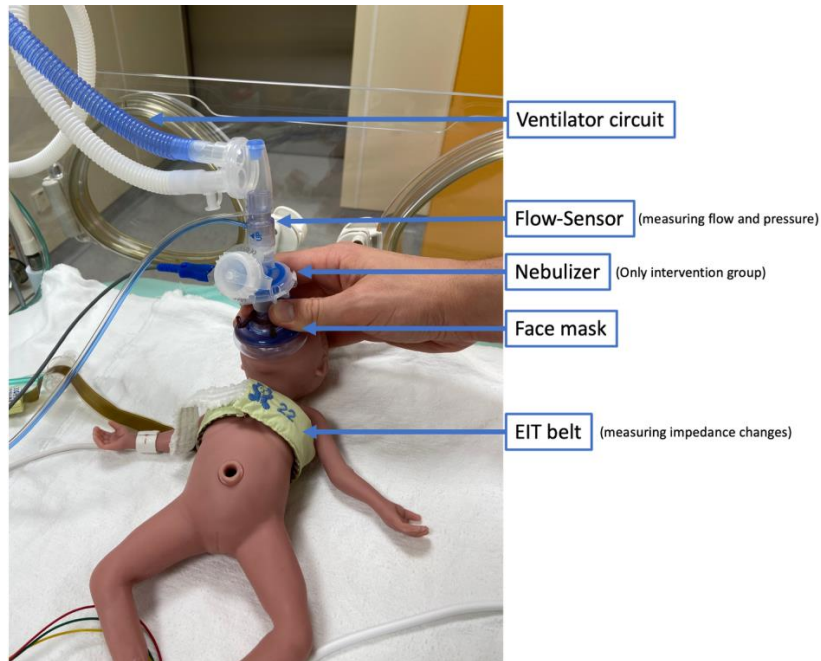
24 hrs	0.66 (0.61 to 0.81)	0.62 (0.6 to 0.72)	0.36	0.85
<i>D) Gravity-dependent silent spaces [%]</i>				
10 min	1.75 (0.96 to 3.48)	1.03 (0.49 to 3.35)	0.38	0.85
20 min	1.81 (0.44 to 3.44)	0.81 (0.55 to 2.54)	0.42	0.85
30 min	1.43 (0.48 to 2.49)	1.63 (0.54 to 3.83)	0.61	0.95
40 min	1.3 (0.3 to 1.94)	1.62 (0.54 to 2.83)	0.42	0.85
50 min	1.29 (0.4 to 3.42)	1.78 (1.06 to 3.62)	0.27	0.85
60 min	0.92 (0.43 to 1.52)	1.52 (0.7 to 3.44)	0.16	0.75
70 min	0.67 (0.41 to 1.07)	0.89 (0.65 to 1.7)	0.53	0.92
80 min	0.54 (0.27 to 2.55)	1.51 (0.95 to 3.21)	0.28	0.85
90 min	0.03 (0 to 1.06)	3.99 (0.54 to 7.49)	0.18	0.77
6 hrs	0.95 (0.7 to 1.44)	0.63 (0.52 to 2.07)	1	1
12 hrs	0.61 (0.21 to 1.47)	0.55 (0.45 to 1.65)	1	1
24 hrs	0.57 (0.26 to 2.75)	1.1 (0.61 to 1.35)	0.54	0.92
<i>E) Non-gravity-dependent silent spaces [%]</i>				
10 min	6.48 (4.55 to 7.93)	7.35 (5.48 to 8.45)	0.32	0.85
20 min	6.25 (3.62 to 8.61)	7.65 (6.08 to 8.6)	0.22	0.85
30 min	6 (4.84 to 7.71)	6.53 (5.05 to 9.35)	0.51	0.90
40 min	5.64 (4.99 to 7.86)	5.58 (4.68 to 7.78)	1	1
50 min	6.39 (4.39 to 8.44)	5.81 (5.14 to 7.1)	0.83	1
60 min	6.3 (5.12 to 8.05)	6.32 (4.95 to 8.48)	0.98	1
70 min	5.56 (4.67 to 6.75)	6.39 (5.86 to 7.29)	0.35	0.85
80 min	7.83 (6.62 to 8.82)	6.62 (4.9 to 8.86)	0.43	0.85
90 min	7.53 (6.16 to 8.53)	7.45 (6.22 to 8.51)	0.90	1
6 hrs	9.6 (7.85 to 11.94)	8.09 (6.34 to 9.35)	0.07	0.58
12 hrs	9.18 (7.36 to 12.05)	6.71 (5.36 to 7.98)	<b>0.027</b>	0.41
24 hrs	8.38 (7.33 to 9.4)	6.24 (5.02 to 8.97)	0.15	0.73

**Supplementary Table S3. Changes in ventilation EIT parameters over time.** Analysis for each timepoint is based only on infants who are non-invasively ventilated at the respective timepoint (see Figure 2 for exact numbers). *Abbreviations:*  $p_{adj}$  = adjusted p-value using the Bonferroni-Holm method.

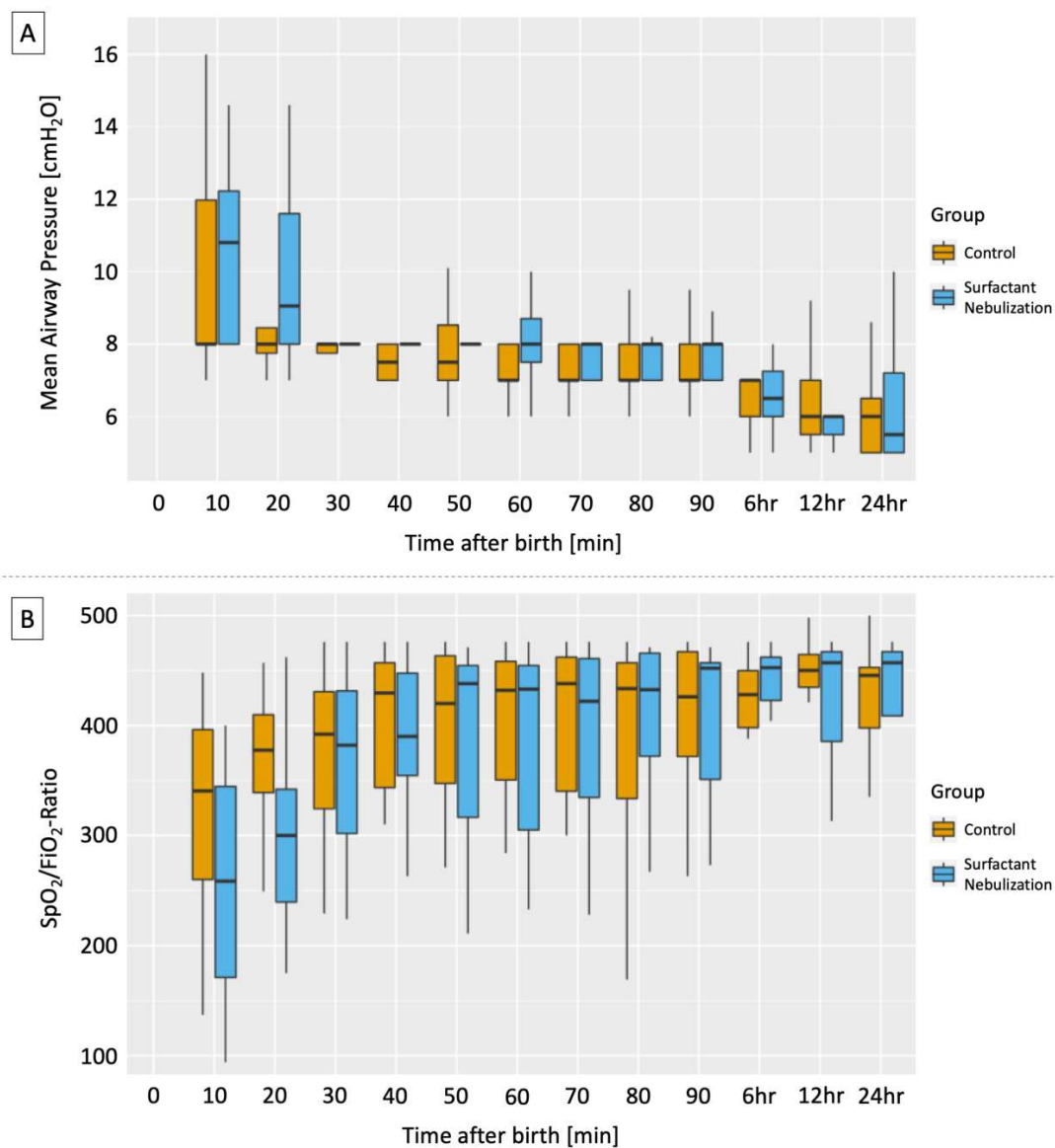
Variable	Surfactant nebulization (N=16)	Standard care (N=16)	p-value	P <sub>adj</sub>
VTe [ml/kg]				
10 min	6.3 (5.9 – 7.5)	5.5 (4.4 – 7.8)	0.25	1
20 min	5.9 (4.5 – 7.1)	5.2 (4.4 – 7.5)	1	1
30 min	5.7 (4.6 – 6.4)	6.5 (4.4 – 7.5)	0.69	1
Leak [%]				
10 min	3 (0 – 12)	3 (0 – 10)	0.98	1
20 min	8 (5 – 11)	5 (4 – 10)	0.42	1
30 min	4 (2 – 7)	2 (0 – 7)	0.54	1
Ti [sec]				
10 min	0.3 (0.3 – 0.32)	0.31 (0.3 – 0.34)	0.76	1
20 min	0.3 (0.3 – 0.34)	0.31 (0.29 – 0.38)	0.69	1
30 min	0.34 (0.3 – 0.42)	0.35 (0.31 – 0.4)	0.95	1
Ti/Te-ratio				
10 min	0.43 (0.41 – 0.45)	0.43 (0.36 – 0.45)	0.70	1
20 min	0.43 (0.43 – 0.44)	0.41 (0.3 – 0.5)	0.59	1
30 min	0.43 (0.43 – 0.61)	0.44 (0.38 – 0.64)	1	1
RR [1/min]				
10 min	66 (57 – 85)	71 (48 – 78)	0.88	1
20 min	61 (56 – 75)	56 (54 – 63)	0.22	1
30 min	61 (57 – 67)	60 (50 – 92)	0.83	1

**Supplementary Table S4. Changes in respiratory function data (N=32).** Abbreviations:  $p_{adj}$  = adjusted p-value using the Bonferroni-Holm method; VTe = expired tidal volume, Ti = inspiratory time, Ti/Te-ratio = ratio of inspiratory and expiratory time, RR = respiratory rate, MAP = mean airway pressure.

## SUPPLEMENTARY FIGURES



**Supplementary Figure S1.** Setup of the devices in the intervention group. The control group had the same setup except the nebulizer.



**Supplementary Figure S2. Mean Airway pressure (A) and SpO<sub>2</sub>/FiO<sub>2</sub>-ratio (B) over the first 24 hours.** The corresponding exact values can be found in Supplementary Table S1. *Abbreviations:* cmH<sub>2</sub>O = centimeters of water, SpO<sub>2</sub> = peripheral oxygen saturation, FiO<sub>2</sub> = fraction of inspired oxygen, min = minutes, hr = hours, SN = surfactant nebulization.

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