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Transcutaneous electromyography of the diaphragm

Monitoring breathing and the effect of respiratory support in preterm infants

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Publication date

2018

Document Version

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Citation for published version (APA):

de Waal, C. G. (2018). *Transcutaneous electromyography of the diaphragm: Monitoring breathing and the effect of respiratory support in preterm infants*. [Thesis, fully internal, Universiteit van Amsterdam].

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Chapter 6

Electrical activity of the diaphragm during nCPAP and high flow nasal cannula

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Archives of Diseases in Childhood – Fetal and Neonatal Edition
2017 Sep;102(5):F434-F438



Abstract

Objective

To determine if the electrical activity of the diaphragm, as measure of neural respiratory drive and breathing effort, changes over time in preterm infants transitioned from nasal continuous positive airway pressure (nCPAP) to high flow nasal cannula (HFNC).

Design

Prospective observational study.

Setting

Neonatal intensive care unit.

Patients

Stable preterm infants transitioned from nCPAP to HFNC using a 1:1 pressure to flow ratio.

Interventions

The electrical activity of the diaphragm was measured by transcutaneous electromyography (dEMG) from 30 minutes before until 3 hours after the transition.

Main outcome measures

At eight time points after the transition to HFNC, diaphragmatic activity was compared with the baseline on nCPAP. Percentage change in amplitude_{dEMG} peak_{dEMG} and tonic_{dEMG} were calculated. Furthermore, changes in respiratory rate, heart rate and fraction of inspired oxygen (FiO₂) were analyzed.

Results

Thirty-two preterm infants (mean gestational age: 28.1 ± 2.2 weeks, mean birth weight: 1,118 ± 368 g) were included. Compared to nCPAP, the electrical activity of the diaphragm did not change during the first 3 hours on HFNC (median (IQR) change in amplitude_{dEMG} at t=180 min: 2.81% (-21.51–14.10)). The respiratory rate, heart rate and FiO₂ remained stable during the 3-hour measurement.

Conclusion

Neural respiratory drive and breathing effort assessed by electrical activity of the diaphragm is similar in the first 3 hours after transitioning stable preterm infants from nCPAP to HFNC with a 1:1 pressure-to-flow ratio.

Introduction

Due to an impaired control of breathing and compromised lung function, most preterm infants need respiratory support during the first weeks of life.¹ Historically, nasal continuous positive airway pressure (nCPAP) has been the preferred mode of non-invasive respiratory support in preterm infants.² nCPAP improves lung function and reduces work of breathing.³ Furthermore, nCPAP is associated with a reduced risk of death or bronchopulmonary dysplasia compared with invasive mechanical ventilation.⁴

Heated humidified high flow nasal cannula (HFNC) is considered a new alternative for nCPAP and is increasingly used over the last few years in neonatal intensive care.^{5,6} Recent studies have suggested that HFNC is as effective as nCPAP in providing respiratory support in patients with respiratory distress syndrome or patients extubated from invasive mechanical ventilation.⁷⁻⁹ Furthermore, HFNC seems to cause less stress and less nasal trauma than nCPAP in preterm infants.⁷⁻¹¹

Despite its increasing popularity, data on the physiological effects of HFNC are limited. Most studies have investigated the association between flow rate and intrapharyngeal or transesophageal pressure, showing conflicting results.¹²⁻¹⁴ The effect of HFNC on work of breathing has been studied using an oesophageal balloon or pressure catheter and no differences between HFNC and nCPAP were reported.^{12,14,15} However, most of these studies included a relatively small number of infants and measured work of breathing only once for a short period of time (< 15 min). This may have impacted these findings.

Electrical activity of the diaphragm measured by electromyography (dEMG) is an objective clinical parameter considered to be a direct measure of neural respiratory drive and breathing effort. Studies have shown that it can be measured invasively using a feeding catheter with miniaturized electrodes or non-invasively using adhesive surface electrodes for transcutaneous measurement.¹⁶⁻¹⁸ This technique can therefore be used to assess breathing effort during weaning from nCPAP to HFNC.

The aim of this study was to determine the changes in the electrical activity of the diaphragm over time in preterm infants transitioned from nCPAP to HFNC using transcutaneous dEMG. We hypothesized that the electrical activity of the diaphragm would not change on HFNC compared with nCPAP.

Methods

Study population

This single-center prospective observational cohort study was conducted at the neonatal intensive care unit of the Emma Children's Hospital, Academic Medical Center Amsterdam, the Netherlands. We included spontaneous breathing preterm infants born with a gestational age (GA) < 34 weeks, recovered from the acute phase of respiratory

distress syndrome, supported with nCPAP and considered eligible for transition to HFNC by the attending physician. Infants with major congenital malformations were excluded. The study protocol was approved by the institutional review board and both parents provided written informed consent.

Study protocol

The study protocol started 30 minutes before and lasted for 3 hours after the transition from nCPAP to HFNC. nCPAP was delivered via one of the following devices: AVEA® (Vyaire, Yorba Linda, California, USA), Infant Flow SiPAP (Vyaire) and Infant Flow NCPAP (Vyaire). The Optiflow junior system (Fisher and Paykel Healthcare, East Temaki, Auckland, New Zealand) was used for HFNC support.

Infants were transitioned from nCPAP to HFNC with a 1:1 pressure-to-flow ratio because some physiological studies have indicated that the association between nCPAP pressure and HFNC flow rates approaches linearity.^{13,14} For example, infants supported with nCPAP 4 cmH₂O were transitioned to HFNC 4 L/min.

During the measurement no nursing procedures, except feeding, were performed. Based on clinical parameters, such as supplementary oxygen need, respiratory distress and cardiopulmonary events, the attending physician could decide to increase the HFNC flow rate in steps of 1 L/min. A failed transition from nCPAP to HFNC was defined as the need to restart nCPAP within 48 hours. This decision was left to the attending physician who was blinded for the dEMG recording.

Electrical activity of the diaphragm was continuously measured by placing three skin electrodes (disposable Kendall H59P Electrodes; Covidien, Mansfield, Massachusetts USA) on the chest of the infant. Two electrodes were placed bilaterally at the costoabdominal margin in the nipple line (frontal diaphragm lead) and the common electrode was placed on the sternum. The electrodes were connected to a portable 16-channel physiological amplifier (Dipha-16, Macawi Medical Systems, Eindhoven, The Netherlands). The measured data were wirelessly transported to a bedside personal computer. The raw electrophysiological signal was digitally transformed into bipolar dEMG signals followed by digital first-order high-pass filtering. After removing the electrical activity of the heart, the so-called gated dEMG signal was averaged as described by O'Brien *et al.*¹⁹ This averaged dEMG signal was used for further analysis. Details on technical aspects of processing of the measured signal are provided elsewhere.^{19,20}

The dEMG signals were on-line recorded and preprocessed at a bedside personal computer. For off-line postprocessing and analysis the data acquisition and processing software package Polybench (Applied Biosignals, Weener, Germany) was used.

Parameters

To analyze the electrical activity of the diaphragm, stable 30-second recordings were selected at nine preset time points; at baseline ($t=-5$ min) on nCPAP and at $t=5, 15, 30, 60, 90, 120, 150$ and 180 min after the transition ($t=0$ min) from nCPAP to HFNC. Stable recordings were defined as no movement or technical artefacts in the dEMG signal. The outcome parameters were calculated automatically as average of all single breaths in the selected recording, containing approximately 30 breaths as recommended in infant lung function testing.²¹

From the dEMG signal the following parameters were calculated. The amplitude_{dEMG} (μV) of the signal, defined as the difference between the highest (peak_{dEMG} (μV)) and lowest (tonic_{dEMG} (μV)) electrical activity within each breathing cycle. Additionally, the inspiratory time ($T_{i\text{dEMG}}$), expiratory time ($T_{e\text{dEMG}}$), respiratory rate and heart rate were extracted from the dEMG signal. $T_{i\text{dEMG}}$ was defined as the time from the lowest point in the dEMG signal to the next maximum and $T_{e\text{dEMG}}$ as the time from a maximum in the dEMG signal to the next minimum. The dEMG parameters are compared with baseline at the eight time points after transition from nCPAP to HFNC and expressed as percentage change (Δ %) over time. Furthermore, the coefficient of variation (CV) of the amplitude_{dEMG}, as representative of the dEMG derived parameters, was calculated at each time point.

At the start of the measurement, the following patient characteristics were documented: GA at birth, birth weight, gender, prior need for mechanical ventilation, surfactant administration, postnatal age and weight at the day of inclusion. During the measurement, changes in body position, HFNC settings and fraction of inspired oxygen (FiO_2) were tracked. Data on transcutaneous oxygen saturation (SpO_2) were recorded every 30 minutes during the measurement period.

Sample size and analysis

In this study, we aimed to include 30 infants which allowed us to detect a minimum difference in electrical activity of the diaphragm of 7% with a power of 80% and a significance level of 5%.

For statistical analysis SPSS V.22.0 (IBM, Armonk, New York, USA) and GraphPad Prism V.5.0 (GraphPad Software, San Diego, California, USA) were used.

Data were expressed as mean \pm SD or median (IQR) depending on their distribution. The calculated dEMG parameters were not normally distributed; therefore, the repeated measurement Friedman's test with post hoc Dunn's test was used to compare these parameters over time. To compare groups, the independent Student's t-test or the Mann-Whitney U test was used. A p value of < 0.05 was defined as statistically significant.

Results

A total of 35 infants were measured during their transition from nCPAP to HFNC, as shown in Figure 1. Of these, three infants were excluded; one measurement had to be stopped because of an acute clinical deterioration due to strangulation of an inguinal hernia, one because of an upper airway obstruction and in one infant reliable dEMG measurement was not possible due to extensive movements. This left 32 infants for the final analysis and their basic characteristics are summarized in Table 1.

Sixty minutes after the transition, data of one infant could no longer be recorded due to connectivity problems of the dEMG device. Data recorded up to that moment were included in the analysis. In four patients, the HFNC flow rate was increased during the measurement with 1 L/min (n=2) or 2 L/min (n=2). Two infants were moved from supine to prone position because of clinical signs of respiratory distress.

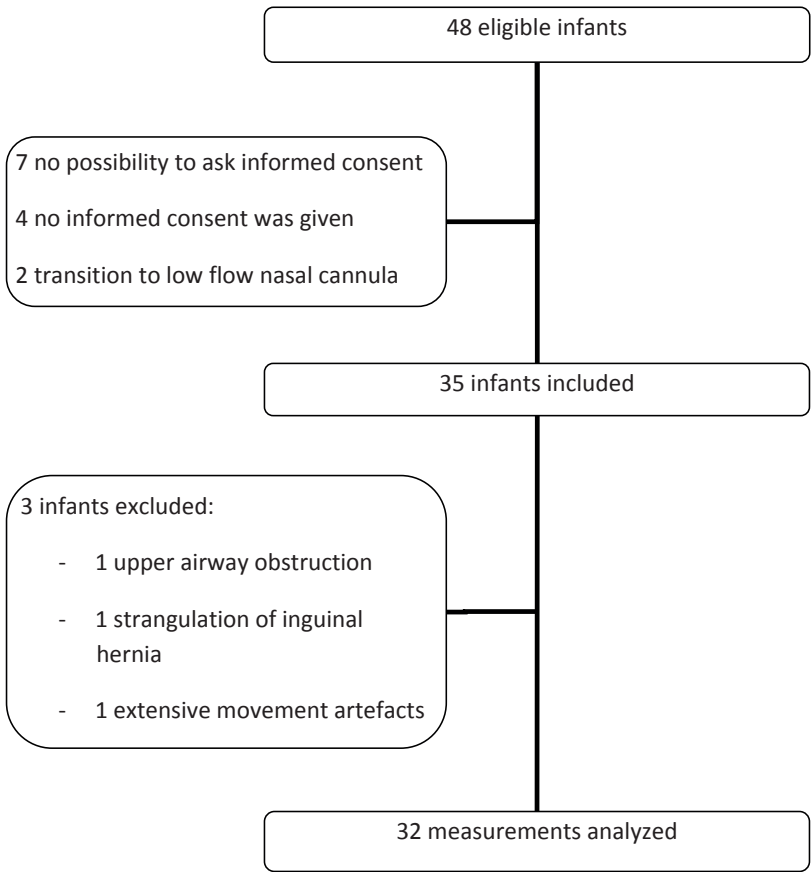


Figure 1. Flow diagram of the study population

Table 1. Baseline characteristics study population

	n=32
Gestational age at birth (weeks)	28.1 ± 2.2
Birth weight (g)	1118 ± 368
Male, n (%)	24 (75)
Antenatal steroids, n(%)	26 (81)
Apgar score at 5 minutes	8 (6 - 9)
Mechanical ventilation, n (%)	11 (34)
Days	6 (1 - 14)
Surfactant, n (%)	14 (44)
Postmenstrual age at measurement (weeks)	31.7 ± 2.1
Postnatal age (days)	17 (6 - 44)
Weight at measurement (g)	1480 ± 494
nCPAP setting	
PEEP (cmH ₂ O)	4 (4 - 4)
FiO ₂ (%)	21 (21 - 24)
HFNC at the end of measurement	
Flow (L/min)	4 (4 - 5)

Mean ± SD or median (IQR). FiO₂, fraction of inspired oxygen; HFNC, high flow nasal cannula; nCPAP, nasal continuous positive airway pressure; PEEP, positive end-expiratory pressure.

dEMG and clinical parameters

The electrical activity of the diaphragm, expressed as percentage change in amplitude_{dEMG'}, peak_{dEMG} and tonic_{dEMG} activity did not change after the transition from nCPAP to HFNC (Figure 2, Table 2). Compared with baseline, the Ti_{dEMG} and Te_{dEMG} decreased marginally after transition from nCPAP to HFNC (Table 2). However, these small changes did not result in a clinically relevant alteration in respiratory rate. The CV of the amplitude_{dEMG} at baseline was 0.34 (IQR: 0.29 – 0.44) and did not change after transitioning to HFNC (Table 2).

No clinically relevant changes were seen in heart rate, SpO₂ and FiO₂ in the 3 hours after transition from nCPAP to HFNC (Table 2).

Table 2. dEMG and clinical parameters over time after transition from nCPAP to HFNC

	Baseline	5 minutes	15 minutes	30 minutes	60 minutes	90 minutes	120 minutes	150 minutes	180 minutes
	n = 32	n = 32	n = 32	n = 32	n = 31	n = 31	n = 31	n = 31	n = 31
<u>dEMG parameters</u>									
Δ Amplitude _{dEMG} (%)	0 (0 - 0)	4.90 (-10.36 - 35.95)	-1.99 (-20.72 - 24.70)	-2.21 (-19.32 - 18.25)	-3.19 (-16.97 - 16.49)	-7.07 (-22.36 - 10.34)	1.82 (-16.67 - 10.67)	-13.57 (-21.69 - 9.04)	2.81 (-21.51 - 14.10)
Δ Peak _{dEMG} (%)	0 (0 - 0)	9.79 (-8.20 - 33.24)	4.04 (-13.97 - 17.33)	-1.28 (-15.51 - 22.67)	3.18 (-13.57 - 26.04)	-2.54 (-11.05 - 17.79)	-0.52 (-11.05 - 13.74)	-9.65 (-25.25 - 7.49)	2.19 (-22.01 - 20.39)
Δ Tonic _{dEMG} (%)	0 (0 - 0)	11.87 (-4.88 - 24.32)	9.23 (-6.04 - 27.35)	6.29 (-7.00 - 35.77)	10.96 (-19.34 - 33.38)	-5.59 (-27.29 - 16.02)	-4.01 (-20.17 - 19.79)	-6.82 (-25.20 - 19.59)	4.97 (-21.48 - 31.46)
CV amplitude _{dEMG}	0.34 (0.29 - 0.44)	0.36 (0.29 - 0.58)	0.33 (0.28 - 0.69)	0.40 (0.29 - 0.59)	0.40 (0.28 - 0.60)	0.47 (0.30 - 0.79)	0.33 (0.29 - 0.48)	0.43 (0.30 - 0.61)	0.42 (0.27 - 0.58)
<u>Clinical parameters</u>									
Respiratory rate (breaths/min)	61 (55 - 69)	67 (57 - 73)	65 (53 - 78)	70 (61 - 74)*	65 (57 - 76)*	64 (59 - 75)	66 (55 - 73)	65 (56 - 77)	67 (57 - 72)
Heart rate (beats/min)	147 (141 - 158)	156 (148 - 162)*	150 (142 - 160)	152 (143 - 162)	148 (140 - 158)	150 (142 - 158)	152 (140 - 162)	152 (142 - 160)	154 (144 - 164)
FI _O ₂	0.21 (0.21 - 0.24)	0.21 (0.21 - 0.25)		0.21 (0.21 - 0.30)*	0.21 (0.21 - 0.30)	0.21 (0.21 - 0.30)	0.21 (0.21 - 0.30)	0.21 (0.21 - 0.31)	0.21 (0.21 - 0.31)
SpO ₂ (%)	96 (93 - 98)	94 (88 - 98)*		94 (91 - 95)	95 (92 - 98)	94 (92 - 96)	94 (91 - 97)	94 (91 - 96)	95 (92 - 98)

Data are expressed as median (IQR). Data on FI_O₂ and SpO₂ were not collected 15 minutes after the transition. FI_O₂ data of one infant were not available. * p<0.05 at time point compared to baseline. CV, coefficient of variation; FI_O₂, fraction of inspired oxygen; HFNC, high flow nasal cannula; dEMG, electromyography of the diaphragm; nCPAP, nasal continuous positive airway pressure; SpO₂, transcutaneous oxygen saturation

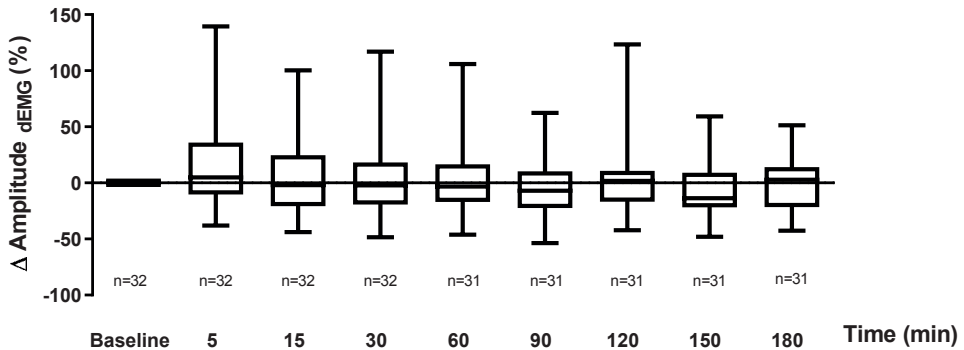


Figure 2. Percentage change in amplitude_{dEMG} at eight time points after transition from nasal continuous positive airway pressure to high flow nasal cannula compared with baseline. Box plots represent median, IQR and range. dEMG, electromyography of the diaphragm; N, number of infants at each time point.

Success versus failure

Of the 32 infants, 8 (25%) failed the transition due to increased oxygen need (n=3) and increased clinical signs of respiratory distress (n=5). Baseline characteristics of infants failing the transition did not differ from infants successfully transitioned (n=24) to HFNC.

The electrical activity of the diaphragm and clinical parameters did not differ significantly between the infants failing the transition and those successfully transitioned to HFNC in the first 3 hours after transition.

Discussion

To our knowledge, this is the largest study so far to assess neural respiratory drive and breathing effort during nCPAP and HFNC in preterm infants. We found similar electrical activity of the diaphragm measured by transcutaneous dEMG in the first 3 hours after transition from nCPAP to HFNC, suggesting a comparable level of support during these two most widely used non-invasive modalities in stable preterm infants. This finding is strengthened by stable clinical parameters after the transition to HFNC in our population.

Physiological studies on HFNC in preterm infants have tried to establish if HFNC provides similar respiratory support as nCPAP. Most of these studies focused on the relation between flow and airway pressure, trying to establish the flow necessary to match nCPAP support.^{12–14,22,23} However, the working mechanism of HFNC is thought to be multifactorial, suggesting that the level of support during HFNC is probably not dependent on airway pressure alone.^{24,25} For this reason, breathing effort might be a better outcome parameter to compare the level of support during HFNC and nCPAP.

In this study we assessed neural respiratory drive and breathing effort by measuring electrical activity of the diaphragm via transcutaneous dEMG. We used a 1:1 pressure-to-flow ratio to set the flow during HFNC after transitioning from nCPAP, based on previous studies suggesting that the relationship between flow and pressure during HFNC approaches linearity.^{13,14} Our study suggests that this pressure-to-flow ratio results in a similar level of support during nCPAP and HFNC. This finding is in line with previous cross-over studies assessing the effect of HFNC and nCPAP on work of breathing measured with an oesophageal balloon.^{12,14,15} These studies reported no differences in work of breathing when comparing different flow rates (2-8 L/min) during HFNC with nCPAP levels of 5-6 cmH₂O.

Nasef *et al*²⁶ measured in a smaller study electrical activity of the diaphragm by transesophageal dEMG in preterm infants crossing over between nCPAP using a mean pressure of 5 cmH₂O and HFNC with a mean flow rate of 5 L/min. Comparable with our results, they did not find differences in diaphragmatic activity between nCPAP and HFNC. However, they found large individual variations in diaphragmatic activity. This was also the case in the present study with a CV of the amplitude_{dEMG} ranging from 33% to 47%. In this study, we also compared clinical parameters such as respiratory rate, heart rate, SpO₂ and FiO₂ before and after transitioning to HFNC. Consistent with our finding on diaphragmatic activity, the clinical parameters did not change over the 3-hour measurement period. These results are also in line with previous reports.

A total of eight (25%) infants failed the transition from nCPAP to HFNC. Secondary analysis revealed no differences in electrical activity of the diaphragm or clinical parameters between infants that failed or were successfully transitioned to HFNC in the first 3 hours after transition. However, the small numbers in both groups prevent firm conclusions on this finding and future studies are needed to answer the question whether diaphragmatic activity could be used to predict HFNC failure.

It is important to acknowledge that most of the studies reporting breathing effort on HFNC had a relatively small sample size and/or measured this outcome parameter only once during a short period of time, relatively early after switching between modes. This may have compromised the validity of the findings. The strength of our study is the relatively large sample size and the longitudinal measurement, providing information on neural respiratory drive and breathing effort at different consecutive time points over a 3-hour period. The fact that our results are consistent with previous reports, adds important strength to the validity of the finding that HFNC provides similar support as nCPAP in preterm infants.

This study has several limitations that need to be addressed. First, we measured diaphragmatic activity up to 3 hours after transition from nCPAP to HFNC. Although this is the longest measurement period so far, changes in diaphragmatic activity may occur after this time period. Future studies should therefore extend the measurement period

to days instead of hours. Second, we only measured the electrical activity of the frontal diaphragm, and not the intercostal muscles as described by Maarsingh et al.²⁰ In preterm infants the intercostal muscles are thought not to have a substantial contribution to breathing effort during tidal breathing²⁷ and therefore we think that the frontal lead of the diaphragm provides sufficient information to describe changes in breathing effort over time. Third, the physiological findings in this study need to be interpreted with caution because transcutaneous dEMG is a relatively new method to measure breathing effort in preterm infants. The studies published on this technique so far have provided valuable information on changes in neural respiratory drive after treatment with caffeine and during weaning from non-invasive respiratory support.^{18,28} However, the number of preterm infants included in these studies does not yet allow for defining normative reference ranges for diaphragmatic activity in this population. Also, further research is needed to investigate the effect of individual variations in diaphragmatic activity before the technique could be introduced as clinical application for titrating respiratory support. Another limitation is that the study did not have a randomized cross-over design, which may be considered a methodological weakness. However, the fact that most infants were in a stable clinical condition and the measurement period was 3 hours, makes it unlikely that physiological changes in breathing effort not related to the change in support, impacted the results. Furthermore, the fact that we measured changes in neural respiratory drive and breathing effort at a time the infant was deemed clinically ready to be transitioned from nCPAP to HFNC might also be considered a strength. In most previous crossover studies, this was not the case and this may have compromised the clinical relevance of the findings. Finally, we included stable preterm infants after the first week of life. The results may differ in less stable infants or at a different postnatal age.

In conclusion, this study shows that neural respiratory drive and breathing effort assessed by electrical activity of the diaphragm is similar in the first 3 hours after transitioning stable preterm infants from nCPAP to HFNC with a 1:1 pressure-to-flow ratio. This adds important physiological evidence that HFNC provides comparable respiratory support as nCPAP. Future studies need to confirm these findings over a longer measurement period and under different clinical conditions.

Acknowledgements

The authors thank Leo A van Eykern for the technical assistance in this study.

What is already known on this topic?

- High flow nasal cannula (HFNC) is increasingly used as an alternative for nasal continuous positive airway pressure (nCPAP) in preterm infants.
- Electrical activity of the diaphragm is a measure for neural respiratory drive and breathing effort.
- Transcutaneous electromyography of the diaphragm (dEMG) can be used in preterm infants and is able to detect changes in diaphragmatic activity.

What this study adds?

- Electrical activity of the diaphragm does not change in the first 3 hours after transition from nCPAP to HFNC in stable preterm infants.
- Clinical parameters as fraction of inspired oxygen and respiratory rate were similar when supported with either nCPAP or HFNC.
- HFNC appears to provide comparable respiratory support as nCPAP in the first 3 hours after transition in stable preterm infants.

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