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Do newborn infants exhale through the CPAP system? Secondary analysis of a randomised cross-over trial

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2022-324462>).

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Received 28 May 2022

Accepted 28 September 2022

Published Online First

19 October 2022

ABSTRACT

Background During nasal continuous positive airway pressure (nCPAP) treatment in neonates, leakage is inevitable and can lead to reduced distending pressure in the lungs of the infant. In current practice, neither leakage nor expiratory flow is measured, which makes it difficult to assess if exhalation is through the device or entirely through leakages.

Objective To examine if infants treated with nCPAP exhale through the CPAP system.

Design and setting Secondary data analyses from the ToNIL trial on leakages during nCPAP treatment. We retrospectively examined respiratory curves for the 50 infants included in the trial, using NI LabVIEW 2015. Each infant was measured with both prongs and nasal masks. A flow recording was classified as exhalation through the system if more than 50% of all expirations showed reverse flow, each for a minimum duration of 0.1 s.

Patients 50 infants were included, born with a mean gestational age (GA) of 34 weeks, median birth weight of 1948 g and mean age at measurement 6.5 days. Inclusion criteria were CPAP treatment and a postmenstrual age (PMA) of 28–42 weeks.

Results In our measurements, 32/50 infants exhaled through the CPAP system in at least one recording with either nasal mask or prongs. Leakages exceeding 0.3 L/min were seen in 97/100 recordings.

Conclusions During nCPAP treatment, infants can exhale through the CPAP system and leakage was common. Measuring expiratory flows and leakages in clinical settings could be valuable in optimising CPAP treatment of infants.

Trial registration number NCT03586856.

INTRODUCTION

Using non-invasive ventilation (NIV) as respiratory support is the standard of care in neonatal settings.^{1,2} Nasal continuous positive airway pressure (nCPAP) is the most widely used support for newborn infants with respiratory distress^{3,4} and has been shown to reduce morbidity and mortality in preterm infants.⁵ Early use of nCPAP is recommended by WHO as an important intervention to reduce neonatal mortality.⁶

There are multiple factors to consider when optimising nCPAP treatment. Clinical studies have focused on the optimal pressure during treatment, devices to use and different strategies when supporting neonates.^{7–10} Recent studies on nCPAP

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ We have not identified studies describing exhalation through the continuous positive airway pressure (CPAP) system in infants.

WHAT THIS STUDY ADDS

⇒ Majority of infants in this study did exhale through the CPAP system. Leakages were common. This is the only study we know that describes exhalation through the CPAP system in infants.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Knowledge on exhalation through the CPAP device is relevant for future studies comparing CPAP systems and interfaces. For clinicians, it could represent an opportunity for optimisation of CPAP treatment.

interfaces and failure of support, have favoured nasal mask over prongs.^{11,12}

Historically, newborn infants were thought to be obligated nose breathers.¹³ This has later been rejected,^{14,15} and more recent trials have shown that infants can breathe through the mouth, making it more correct to describe them as preferred nose breathers.¹⁶

Even if infants prefer to breathe through the nose, we have not identified any studies that report infants actually exhaling through the nasal interface when treated with CPAP systems. The majority of nCPAP systems intended for neonatal use do not measure leakage or expiratory flow. In clinical settings, it is difficult to know if exhalation is through the nCPAP device or solely through leakage. Research on this topic could lead to improvements in nCPAP support providing details for improved management as well as interfaces and device design.

In the ToNIL cross-over trial, we measured absolute leakage for prongs and nasal masks in 50 infants on nCPAP (online supplemental file 1).¹⁷ We observed lower leakages with prongs and large variations in the degree of leakage between infants and between the two interfaces. The recorded flows from the ToNIL trial also allow us to measure expiratory flows and to determine if there is exhalation through the nCPAP system.

The aim of this study was to measure if infants exhale through the nCPAP system.



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To cite: Gunnarsdottir K, Falk M, Baldursdottir S, et al. *Arch Dis Child Fetal Neonatal Ed* 2023;**108**:F232–F236.

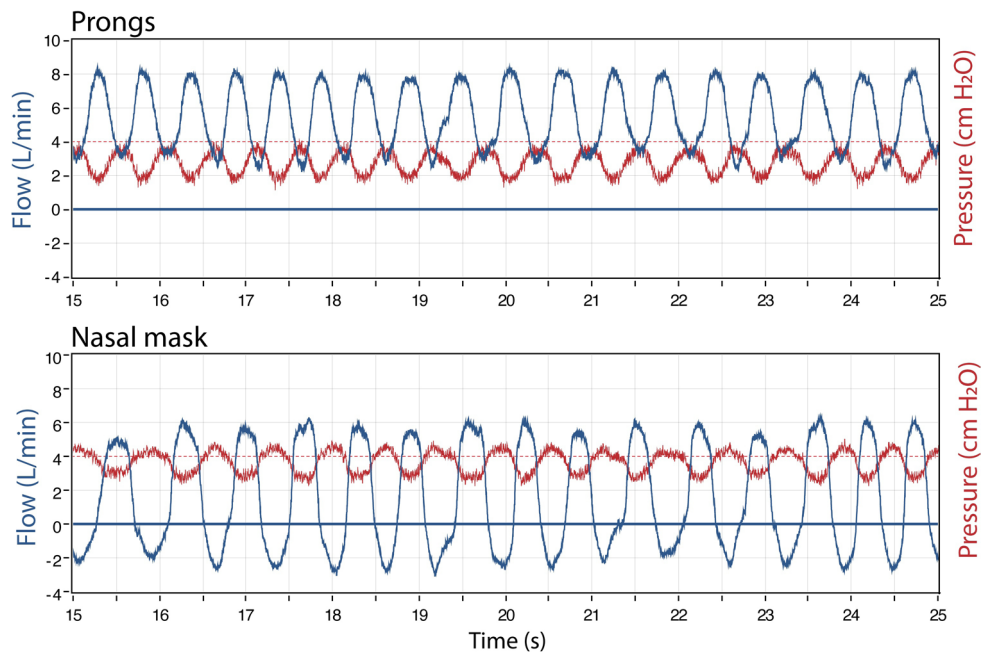


Figure 1 Examples of recordings from an infant that exhaled through the CPAP with nasal mask but not with prongs. With prongs, the fresh gas flow was 6.61 L/min, delivered CPAP was 2.74 cmH₂O and the recorded leakage was 5.4 L/min. No exhalation through the CPAP device was seen. With nasal mask, the fresh gas flow was 6.64 L/min, CPAP was 3.63 cmH₂O and recorded leakage was 1.5 L/min. The infant expired through the CPAP system in all breaths. With low leakage (nasal mask), the pressure at the device during exhalation was higher than the set CPAP of 4 cmH₂O (red dashed line). This infant was born after vaginal delivery, at a gestational age of 41+4 w+d and a birth weight of 3605 g. At the time of recording, the infant was 9 hours old, received nCPAP support for transient tachypnea of the newborn at 4 cmH₂O with FiO₂ 0.21 and had a saturation 98%. The graphs display 10 s of the original 30 s recordings. The reported mean values are from 30 s. nCPAP, nasal continuous positive airway pressure.

MATERIALS AND METHODS

This is a secondary analysis of data from our randomised cross-over trial (ToNIL) that compared leakage during CPAP with two types of interfaces. The study population consisted of 50 infants recruited at two hospitals in Sweden, Östersund Hospital and Karolinska University Hospital in Stockholm. The inclusion criteria were nCPAP treatment with stable, spontaneous breathing and a postmenstrual age (PMA) >28 weeks. Exclusion

criteria were respiratory or cardiac malformations, facial injuries, FiO₂>0.5, recent surgery, circulatory instability or if the infant was recently extubated. Informed parental consent was obtained before inclusion.

The primary outcome was leakage measured in L/min and the site of leakage (through mouth or at the interface) was not determined. For each infant, the fresh gas flow and expiratory flow with both nasal prongs and nasal mask were measured using the flow-through technique,¹⁸ resulting in a total of 100 recordings.

Table 1 Demographic data and characteristics of study participants

Participants, n	50
Male, n (%)	29 (58)
Female, n (%)	21 (42)
GA at birth, w+d	
Mean (SD)	34+0 (4.9)
PMA at study—full weeks	
Median (IQR)	33 (32–38)
PNA age, days	
Median (IQR)	1 (0–4)
Weight, g	
Median (IQR)	1948 (1517–3442)
FiO ₂ , %	
Median (IQR)	21 (21–21.3)
Saturation, %	
Mean (SD)	97 (3)
CPAP level, cmH ₂ O	
Mean (SD)	4.0 (0.7)
CPAP duration, hours	
Median (IQR)	31 (9.8–96.8)
CPAP, continuous positive airway pressure; GA, gestational age; PMA, postmenstrual age; PNA, postnatal age.	

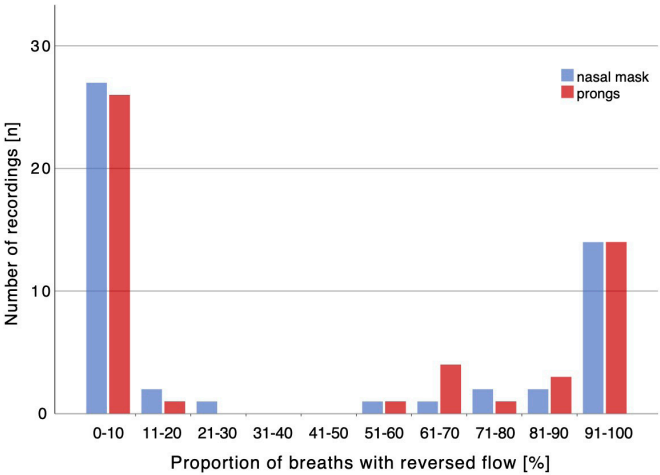


Figure 2 Proportion of breaths with reversed flow for the 50 recordings with nasal mask and the 50 recordings with prongs. In 43 of 100 measurements, most of the recorded breaths revealed exhalations through the nasal continuous positive airway pressure system (bars to the right, >50% of breaths).

Table 2 Comparison of exhalation through nCPAP for the two interfaces

	Exhaled mask n=20	Not exhale mask n=30	P value	Exhaled prongs n=23	Not exhale prongs n=27	P value
GA birth, days (median (IQR))	33+2 (31+2 to 37+6)	33+1 (31+3 to 39+3)	0.937	35+3 (31+4 to 39+3)	32+6 (30+0 to 35+4)	0.087
PMA, days (median (IQR))	33+4 (31+5 to 38+1)	33+4 (32+2 to 39+4)	0.566	35+3 (31+5 to 39+4)	33+3 (32+1 to 35+6)	0.316
Postnatal age, days (median (IQR))	1 (0 to 4)	1 (1 to 4)	0.451	1 (0 to 1)	3 (1 to 4)	0.015
Weight, g (median (IQR))	1864 (1469 to 3386)	2017 (1584 to 3420)	0.736	2522 (1744 to 3705)	1714 (1302 to 2196)	0.017
CPAP duration, hours (median (IQR))	20 (8 to 95)	33 (13 to 100)	0.276	18 (8 to 33)	60 (13 to 144)	0.018
CPAP level, cmH ₂ O (median (IQR))	4 (4 to 4)	4 (4 to 5)	0.115	4 (4 to 4)	4 (4 to 5)	0.247
Respiratory rate, /min (median (IQR))	72 (65 to 88)	74 (59 to 82)	0.643	81 (55 to 100)	73 (59 to 90)	0.690
Leakage, L/min (median (IQR))	0.7 (0.4 to 1.3)	4.3 (2.5 to 6.1)	<0.001	1.1 (0.7 to 1.7)	2.7 (2.4 to 4.0)	<0.001
Peak expiratory flow (median (IQR))	-1.8 (-2.7 to -1.5)	0.6 (-0.3 to 1.7)	<0.001	-2.4 (-4.3 to -1.4)	0.5 (-0.1 to 1.6)	<0.001

Negative peak expiratory flow indicates reversal of flow and exhalation through the system. Mann-Whitney U test used for comparisons. GA, gestational age; nCPAP, nasal continuous positive airway pressure.

The flow-through technique was first described by Rigatto and Brady in 1972.¹⁸ It is used to determine absolute leakage and zeroing flow measurement devices. It has a high precision but the non-linearity and effects of humidity give a small error (<5%) which requires calibration.

After calibration with correct oxygen level, we added two custom-made SFM-3200-60-AW flow metres to the patient circuit, one on the fresh gas limb and another on the patient expiratory limb. The distal flow metres were zeroed against the fresh gas flow, while the interface connected was occluded. With this flow-through technique, there is no extra dead space added to the respiratory circuit.¹⁹

Details of the used methods and CONSORT diagram is available in online supplemental file 2 and in the original publication.¹⁷

Each measurement was 30 s long and was recorded while the infant was calm and breathing quietly. The nCPAP system was attached with prongs or nasal mask in a random order by an experienced nurse blinded to the measured leakage and pressure. During recording, the infant could be in an incubator, in a cot or skin-to-skin with either parent. All measurements were performed with devices of the original infant flow design (nFlow, Intersurgical, Berkshire, UK, or Inspire nCPAP, Inspiration Healthcare, Leicester, UK). All infants received humidified warm air during measurements. Respiratory curves were analysed retrospectively, using National Instruments LabVIEW 2015. Infant breathing and leakages were measured by subtracting the nCPAP device expiratory flow from the fresh gas flow. The system was calibrated and zeroed before each measurement. With no breathing and no leakage, the sum of flows was zero. With leakage, the flow curve was offset upwards. During breathing, the curve crossing zero (ie, a negative flow value) indicated that exhalation was through the CPAP system to some extent (figure 1). To determine if an infant was exhaling through the system, the

respiratory recordings needed to show flow reversal in more than 50% of all breaths, each for a minimum duration of 0.1 s, during a 30 s recording. If all these criteria were met, the infant was considered as having exhaled through the CPAP system. We found no definition of exhalation based on measurement of flow and the selected cut-off values have not been used before.

Expiration through the CPAP system was not defined or registered as an outcome before starting the trial.

Statistical analyses were performed in SPSS V.27. Demographic data for study subjects were summarised using descriptive statistics. Outcome variables were reported as means (±SD) or median (IQR). Group comparisons were conducted using Mann-Whitney U tests, chosen because of skewed distributions in variables in both groups. A p value of <0.05 was considered statistically significant.

RESULTS

All 50 infants were stable during measurements, with low oxygen demand. Background information is provided in table 1. There were no adverse events and measurements were well tolerated. The median time for study measurements and switching between interfaces for each patient was 25 min (IQR 21–30).

The majority, 32/50 neonates, met our criteria of exhalation through the nCPAP system in more than 50% of all breaths in at least one of the two recordings (nasal mask or prongs), and 18/50 did not. Since infants exhaling through the CPAP system with one interface did not necessarily exhale when measured with the other interface, this resulted in 43/100 recordings showing exhalation through the system (figure 2). In the remaining 57 recordings, exhalation through the CPAP was less than 50% of exhalations or did not reach a minimum length of 0.1 s. Leakages exceeding 0.3 L/min were seen in 97/100 measurements, with a maximum leakage of 9.9 L/min. In recordings where the infant

Table 3 Comparison of infants that exhaled through the CPAP system in either interface and those who did not

	Exhaled through either interface (mask or prongs) n=32	Did not exhale via CPAP n=18	P value
GA birth, w+d (median, IQR)	34+0 (31+5–39+2)	32+4 (28+3–35+5)	0.182
PMA, days (median, IQR)	34+0 (31+6–39+3)	33+3 (32+1–36+0)	0.701
Postnatal age (median, IQR)	1 (0–2.8)	2.5 (1–8)	0.029
Weight, g (median, IQR)	2011 (1536–3485)	1734 (1275–2575)	0.249
CPAP duration, hours (median, IQR)	20 (8–67)	60 (16–336)	0.018
CPAP level, cmH ₂ O (median, IQR)	4 (4–4)	4 (4–5)	0.299

Mann-Whitney U test used for comparisons. CPAP, continuous positive airway pressure; GA, gestational age; PMA, postmenstrual age.

exhaled through the nCPAP, leakages were lower ($p < 0.01$, table 2).

When comparing the 32 infants who exhaled through the nCPAP at any time with those who did not, infants who exhaled through the system had a shorter median duration of CPAP treatment and lower median postnatal age (table 3).

Analysing this for each interface showed no difference between groups when recorded with nasal mask, but for prongs recordings more exhalations were seen with lower postnatal age, higher weight and shorter duration of CPAP treatment (table 2).

DISCUSSION

In this secondary analysis of infants in the ToNIL trial, we examined exhalation through the CPAP system. The main finding was that exhaling through the system is common and related to low leakage (table 3). Using flows to determine the proportion of infants exhaling through the CPAP system has not previously been reported.

The relation between exhaling through the system and leakage was expected. For infants not exhaling through the system, leakage was greater than the expiratory flow and exhalation was entirely through leakage. The cause of leakage could not be determined and could have been at the interface, through the mouth or to the oesophagus. The recordings were performed after application by a nurse, unaware of the delivered pressure or leakage. We have previously reported that leakage could be reduced with simple manoeuvres by an investigator guided by the measured leakage. Such guided manoeuvres could result in more infants exhaling through the system (online supplemental file 1).¹⁷

Comparison of infants that exhaled through the nCPAP and those who did not revealed no differences in GA or BW. There was a difference in postnatal age and CPAP duration between the groups (table 3), but when dividing the group based on interface this difference was significant for prongs but not for mask.

A common recommendation in CPAP care is to use well-fitting interfaces to minimise leakage and deliver an effective distending pressure in combination with attentive care to avoid nasal damage.²⁰ Studies on leakage during CPAP treatment are few and no previous studies with blinded application of CPAP systems have been identified.

In a study from 2005, De Paoli *et al*²¹ investigated mean pharyngeal pressure and mouth closure in 11 preterm infants treated with bubble CPAP (bCPAP). They report a reduction in mean pressures delivered to the pharynx compared to at the interface depending on if the mouth was closed or open. They observed that the mean pharyngeal pressures never exceeded the mean set CPAPs and there was always some pressure loss regardless of mouth position. They concluded that it was unlikely that infants exhale through the system and that nCPAP is unlikely to increase expiratory resistance. Their reported average loss of pressure corresponds to our finding that mean leakage was high and that few patients have no leakage. We believe that measuring flows gives a more accurate description when examining exhalation, compared with measuring pressures.

The clinical evidence for using well-fitting interfaces and minimising leakage is low but widely acknowledged as a part of delivering quality care for infants receiving CPAP. In our study, we used a conventional low resistance CPAP system with short binasal prongs or nasal mask. The infant flow device used is pressure stable and easy to exhale through. The function has been described as a fluidic-flip,²² with gas entrainment from a jet that can 'flip' between inspiration and expiration. Compared with

other devices, this could have facilitated exhalation through the device.

When using interfaces that are not designed to provide a snug fit and have high expiratory resistance, it is important to bear in mind that these interfaces are not likely to allow exhalation through the CPAP system under any circumstance. An example of this is the RAM cannula which is sometimes used with CPAP devices off label.²³ There are also examples of systems with short wide nasal prongs and nasal masks designed to be well fitting without leakage where the CPAP generator connected to the interface has high resistance.²⁴ We believe that exhalation through these devices is less common but this was not examined in this study. If CPAP care and outcomes can be improved by minimising leakage and increasing exhalation through the CPAP system remains an open question.

Limitations

We used a CPAP system with low resistance and interfaces designed to fit without leakage.⁹ Other CPAP systems and interfaces might give different results. There was no available definition of what constitutes exhalation through a CPAP system. In our study, we arbitrarily defined exhalation through the system as the device expiratory flow exceeding the fresh gas flow for more than 0.1 s in more than 50% of expirations. The study was small and a major limitation was that the recordings were short. Even if the nurses were blinded to leakage measurements, the results reflect point prevalence in an experimental situation and recordings of hours or days during routine care would be of value.

CONCLUSION

During nCPAP treatment, infants treated with nCPAP can exhale through the CPAP system. For preclinical research, this is relevant for studies comparing CPAP systems and interfaces. For clinicians, it could represent an opportunity for optimisation of CPAP treatment by improving delivery of distending pressures. Using flows to determine exhalation through the CPAP system has not previously been reported.

Contributors KG: study design, data collection, data and manuscript writing, statistical analysis and review. MF: study design, equipment development, data collection, manuscript writing and review. TD: Study design, equipment development, manuscript writing, review and overall content guarantor. SB, SD: study design, data collection, manuscript writing and review. BJ: study design, data interpretation, manuscript writing and review.

Funding The study was funded by the Swedish government, Swedish Lung Heart foundation, Stiftelsen Samariten, Region Stockholm ALF agreement (2020-0302) and Clinical Research Appointment (DNR RS 2019-1140).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Swedish Ethical Review Authority, reference number 2016/2449-3. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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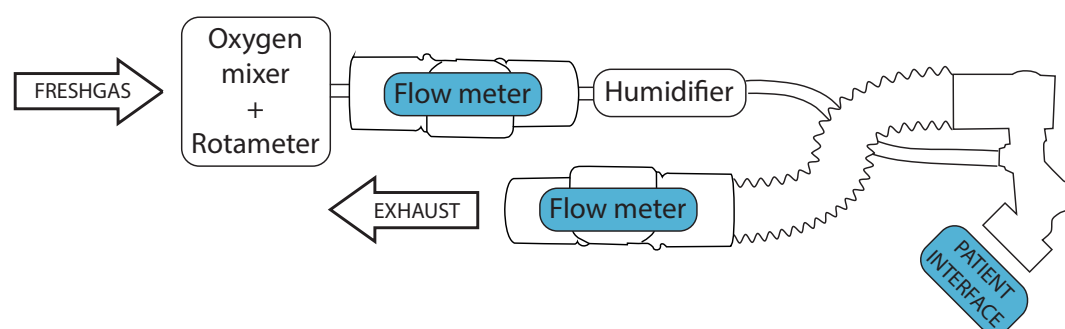
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Supplemental file 1

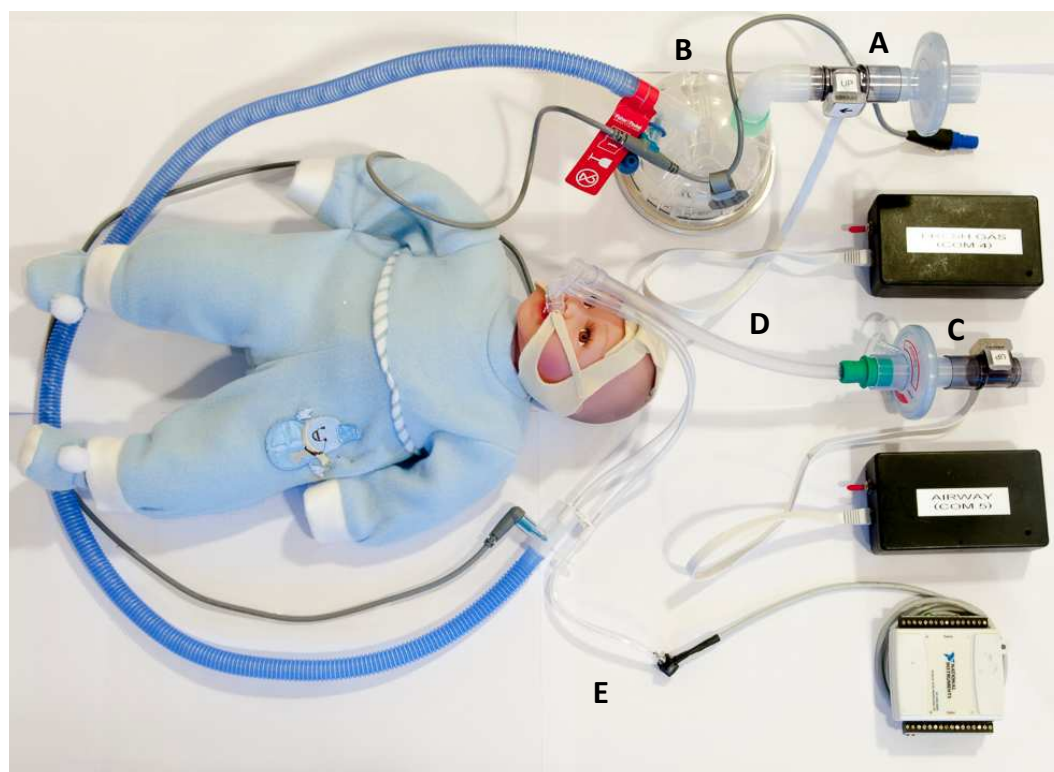
Equipment setup with flow through flow meters

The CPAP driver was replaced with an oxygen mixer and a rotameter to avoid automatic changes in flow with leakage compensation. The fresh gas was humidified using a MR850 humidifier (Fisher & Paykel, New Zealand) and connected to an Infant Flow design device. Two custom SFM-3200-60-AW flow meters (Sensirion AG, Staefa, Switzerland) were added to the patient circuit enabling flow-through measurements; one on the fresh-gas supply and the second on the patient expiratory limb. The configuration added no dead space and minimal resistance.

The flow meters were calibrated with the correct oxygen level and conditioned gas. A calibrated Honeywell pressure sensor (40PC001B1A; Honeywell, Freeport, IL, USA) was used to set the prescribed CPAP. For each interface, connectors were checked for leakage and the flow meters zeroed against each other.



Supplemental figure 2a: Drawing of flow through setup. The fresh gas flow meter (top) is situated on the inspiratory limb and the exhaust flow meter (bottom) is situated on the expiratory limb. The patient interface is positioned between the two flow meters. The same flow meter layout (positioned on inspiratory and expiratory limb) is common in ventilators. By subtracting the expiratory limb flow from the fresh gas flow, the patient flow can be determined. The patient flow represents both leakage and breathing. Illustration published as supplement in the ToNIL trial.(1)

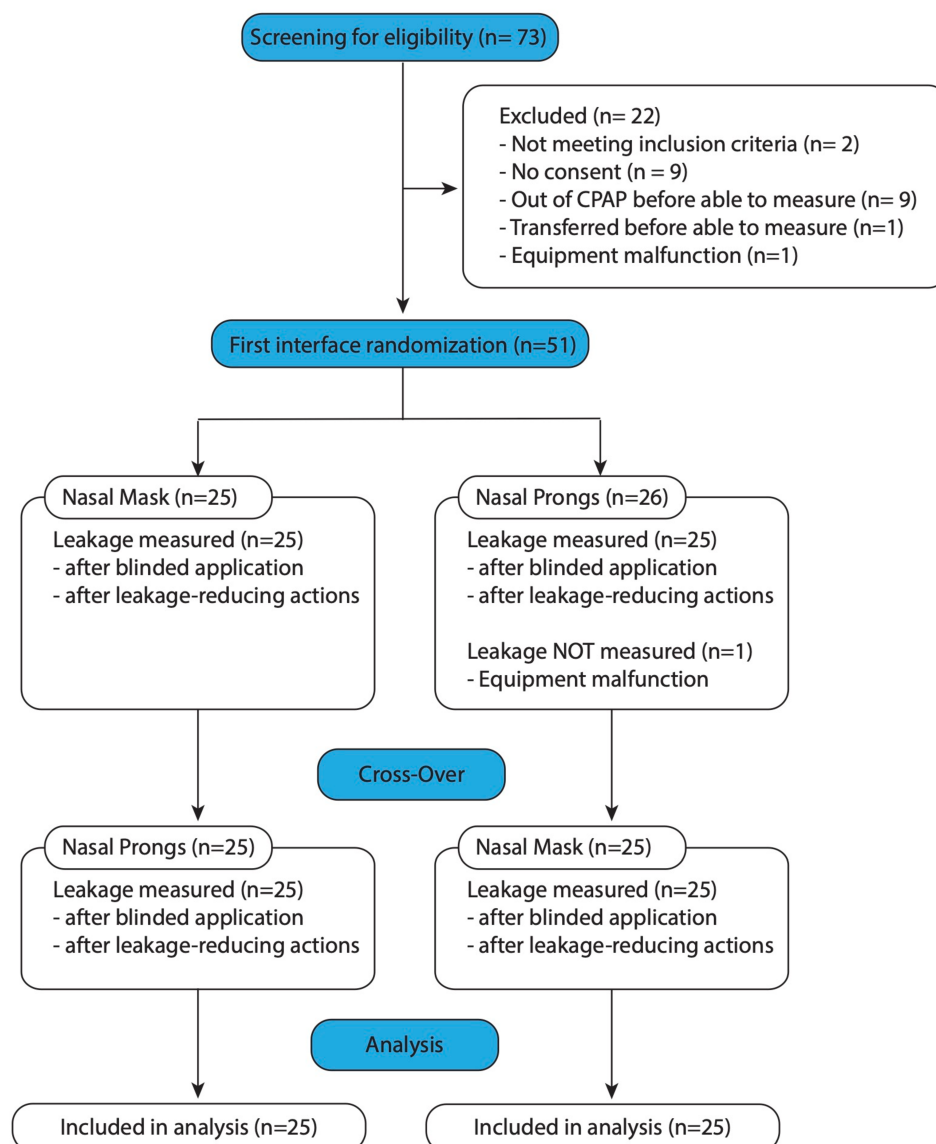


Supplemental figure 2b: The components and layout. The fresh gas flow meter (A) is situated on the inspiratory limb before the humidifier (B). The exhaust flow meter (C) is situated on the expiratory limb (D). The pressure transducer is connected to the CPAP device (E).

1. Falk M, Gunnarsdottir K, Baldursdottir S, Donaldsson S, Jonsson B, Drevhammar T. Interface leakage during neonatal CPAP treatment: a randomised, cross-over trial. *Arch Dis Child Fetal Neonatal Ed*. 2021;**106**:663-7 doi: 10.1136/archdischild-2021-321579.

Supplement 2

CONSORT diagram from the ToNIL trial



Falk M, Gunnarsdottir K, Baldursdottir S, Donaldsson S, Jonsson B, Drevhammar T. Interface leakage during neonatal CPAP treatment: a randomised, cross-over trial. *Arch Dis Child Fetal Neonatal Ed*. 2021;**106**:663-7 doi: 10.1136/archdischild-2021-321579.