Stimulating and maintaining spontaneous breathing of preterm infants at birth

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CHAPTER 4

Time to achieve desired fraction of inspired oxygen using a T-piece ventilator during resuscitation of preterm infants at birth

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ABSTRACT

AIM

To determine the time between adjustment of fraction of inspired oxygen (FiO_2) at the oxygen blender and the desired FiO_2 reaching the preterm infant during respiratory support at birth.

METHODS

This observational study was performed using a Neopuff™ T-piece Resuscitator attached to either a test lung (during initial bench tests) or a face mask during the stabilization of infants at birth. FiO_2 was titrated following resuscitation guidelines. The duration for the desired FiO_2 to reach either the test lung or face mask was recorded, both with and without leakage. A respiratory function monitor was used to record FiO_2 and amount of leak.

RESULTS

In bench tests, the median (IQR) time taken to achieve a desired FiO_2 was 34.2 (21.8 – 69.1) s. This duration was positively associated with the desired FiO_2 difference, the direction of titration (upwards) and the occurrence of no leak (R^2 0.863, F 65.016, $p<0.001$). During stabilization of infants (median (IQR) gestational age 29^{+0} (28^{+2} – 30^{+0}) weeks, birthweight 1290 (1240 – 1488) grams), the duration (19.0 (0.0 – 57.0) s) required to reach a desired FiO_2 was less, but still evident. In 27/55 (49%) titrations, the desired FiO_2 was not achieved before the FiO_2 levels were again changed.

CONCLUSION

There is a clear delay before a desired FiO_2 is achieved at the distal end of the T-piece resuscitator. This delay is clinically relevant as this delay could easily lead to over- and under titration of oxygen, which might result in an increased risk for both hypoxia and hyperoxia.

INTRODUCTION AND RATIONALE

The transition to life after birth is hampered in preterm infants due to the immature respiratory system expressed by poor compliance of the lungs, weakness of the respiratory muscles and an immature respiratory center with a weak respiratory drive. (1) Most preterm infants need respiratory support after birth to aerate their lungs and gain adequate oxygenation.(2) A T-piece ventilator that administers continuous positive airway pressure (CPAP) or positive pressure ventilation (PPV) via face mask is currently the method of first choice in order to minimize lung injury.(2-4) Additional oxygen is often used to reach and maintain adequate oxygenation.(5)

During stabilization after birth, additional oxygen needs to be titrated based on recommended oxygen saturations (SpO_2) to decrease the risk of hypoxia and hyperoxia. (3, 6) Hypoxia may lead to delayed cellular damage, as during hypoxia the production of free radicals will be provoked by an elevated level of hypoxanthine.(7, 8) On the other hand, free radical production (associated with both oxidative and nitrosative stress) also increases during hyperoxia, which can overwhelm the relatively immature antioxidant capacity of the preterm infant.(9-12) The excess of free radicals in turn may cause wide-spread damage to cells, enzymes, lipids, DNA and proteins.(9-12)

A time-dependent oxygen saturation range is targeted during stabilization, that is based on previously described international normograms.(6) To achieve oxygen saturations in this range, neonatal resuscitation guidelines recommend commencing resuscitation with a fraction of inspired oxygen (FiO_2) of 0.21 - 0.3.(3) The desired oxygen concentration is achieved by mixing oxygen and room air using an oxygen blender, from which the gas mixture is administered to the neonate via the T-piece ventilator. During stabilization after birth, infants are evaluated every 30 s, which guides the amount of support and titration of additional oxygen.(3) The study of Goos et al.(5) showed that the FiO_2 needed during stabilization at birth is highly variable between infants, with a reported range of 0.21 – 0.99, with 7 (3 – 10) adjustments of FiO_2.

While the adjustment of FiO_2 is performed at the oxygen blender, this is located upstream of the T-piece resuscitation device and simply alters the concentration of oxygen entering the device. However, it is unknown how long it takes for the gas mixture with the desired oxygen concentration to reach the infant at the distal part of the circuit. As such, further titration could take place before the original desired FiO_2 of gas entering the infant has been achieved. This, in turn, could lead to an increased risk of hypoxia or hyperoxia.

The aim of this study was therefore to determine the time between adjustment of FiO_2 at the oxygen blender and the desired FiO_2 reaching the preterm infant during respiratory support at birth.

METHODS

An observational study was conducted at the Neonatal Intensive Care Unit of the Leiden University Medical Center. The study consisted of two parts: a bench test and clinical observations of neonatal stabilization at birth.

The resuscitation of preterm infants at birth was replicated during a bench test, using a Neopuff™ T-piece Resuscitator (Fisher & Paykel Healthcare, Auckland, New Zealand) attached to a 50 mL test lung (Dräger, Lübeck, Germany). The circuit was set up with a flow of 8 L/minute, positive end expiratory pressure (PEEP) of 8 cm H_2O, and a peak inspiratory pressure (PIP) of 20 cm H_2O. FiO_2 was measured at two distinct positions at the circuit, using oxygen analyzers (Teledyne, Analytical Instruments, USA): proximally - at the outlet of the Neopuff™, and distally – between the T-piece of the Neopuff™ and the test lung (Figure 1). In the clinical part of the study, the same circuit was connected to a face mask (Fisher & Paykel Healthcare, Auckland, New Zealand) instead, which was placed over the mouth and nose of a preterm infant.

During the bench test, FiO_2 was increased from 0.3 to 0.5 to 1.0, and decreased to 0.8, 0.5, 0.3 and 0.21. The time needed to reach the desired FiO_2 at the test lung was recorded, whereby a margin of 0.05 difference between FiO_2 at the proximal and distal part of the circuit was accepted. Mask ventilation without any leakage is difficult to accomplish in clinical practice and leak percentages of 50% are not uncommon.(13) As the amount of flow passing the Neopuff™ circuit and reaching the test lung might be influenced by the amount of leak of the circuit, we performed the bench test both with a leakage of 50% and without any leakage. Leak was created by using a small tube through which some of oxygen/air mixture could flow away. This tube was placed between the Neopuff™ circuit and the test lung. The amount of leakage was ascertained by using a Respiratory Function Monitor (RFM). Both tests (with and without leak) were performed 6 times.

During stabilization of infants, local resuscitation guidelines were followed for increasing FiO_2, using the same increments as those used during the bench test: FiO_2 was started at 0.3, and increased to 0.5 and 1.0 if SpO_2 remained below international normograms.

(6) In addition, FiO_2 was decreased whenever SpO_2 exceeded 90% to 0.8, 0.5, 0.3 and 0.21. Again, we analyzed the time delay between titration of FiO_2 at the proximal part of the circuit and the desired FiO_2 being achieved at the distal part, accepting a difference of 0.05 between those measurements. The amount of leakage was taken into consideration when analyzing the results.

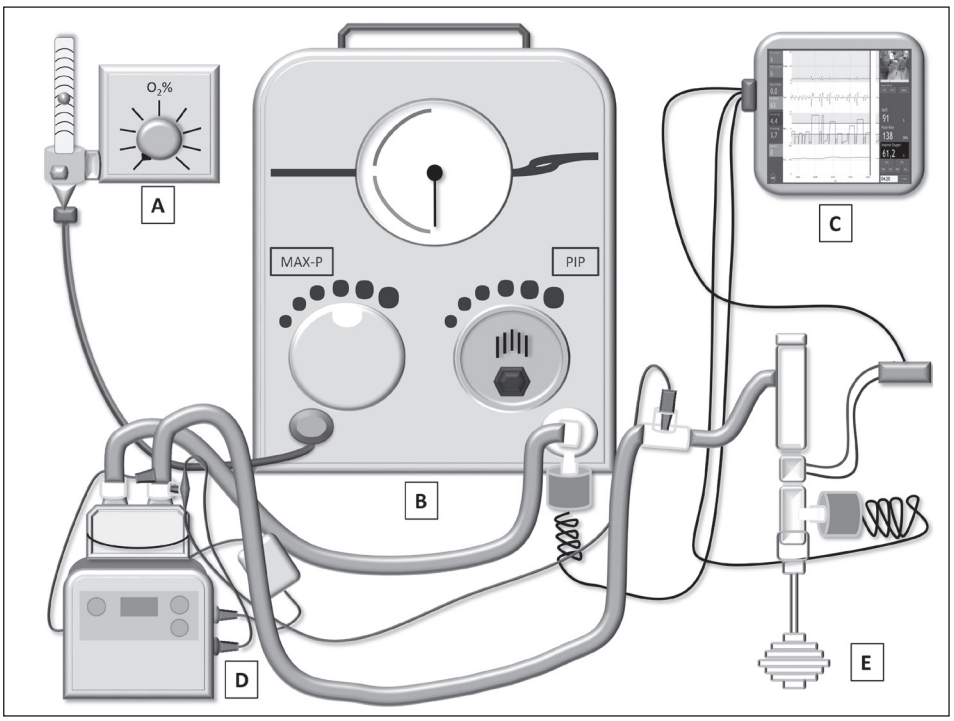

Figure 1 | Set-up bench test

In both parts of the study, a RFM was used for recording FiO_2 at both positions within the circuit, as well as clinically relevant physiological parameters such as oxygen saturation and respiratory function. The RFM uses a small (dead space 1 mL) variable orifice flow sensor (Avea Varflex Flow Transducer, Carefusion, Yorba Linda, CA, USA) to measure gas flow in and out of a face mask, thereby calculating inflation pressures, flow and tidal volumes. The difference between inspired and expired tidal volume estimates leak from the face mask, which was also recorded. Oxygen saturations and heart rates were measured with a Masimo SET pulse oximeter (Masimo SET, Masimo Corporation, Irvine, California, USA). A pulse oximetry probe was placed around the

ulnar aspect of the infant's right wrist. All signals measured were recorded at 200 Hz using the NewLifeBox-R physiological recording system with Polybench software (Applied Biosignals, Weener, Germany). Oxygen analyzers were calibrated at the start of every test and clinical observation.

Data of both parts of the study was analyzed using Microsoft Excel (Microsoft Corporation, Washington, United States). During stabilization of infants, FiO_2, SpO_2 and respiratory function were recorded at 0.5 second intervals. Significant leak was accepted as being > 50% face mask leak. In the event that titration proceeded before the desired FiO_2 from the previous titration (set at the proximal part of the Neopuff™ circuit) had reached the infant (at the distal part of the circuit), the time between titrations was recorded as duration of achieving the desired FiO_2.

Statistical analysis was performed with SPSS version 23.0 (IBM software, NY, USA, 2015). Data is presented as mean ± SD of parametric outcome parameters, non-parametric outcome parameters are presented as median (IQR). Assessment of the relationship between duration of achievement of desired FiO_2, with the difference in FiO_2 that was aimed for during titration and the occurrence of leak, was determined using multiple regression. P-values <0.05 were considered statistically significant. Reported p-values are two-sided.

This was an observational study and as such under the Dutch law on Medical Research in Humans, no specific consent from an ethics committee was required. Nevertheless, the Research Ethics Committee of the Leiden University Medical Center issued a statement of no objection.

RESULTS

Bench test

When adjusting the FiO_2, the oxygen analyzer at the proximal part of the circuit reached the desired oxygen concentration within 3 ± 1 seconds, independent of the amount of leakage in the circuit. There was a delay in time to achieve desired FiO_2 at the distal part of the circuit (median (IQR) duration 34.2 (21.8 – 69.1) s).

Without mask leak, the median (IQR) duration of the FiO_2 to reach the desired concentration at the distal part of the Neopuff™ circuit during up-titration was 58.2 (35.7 - 86.1) s. The largest delay in reaching the desired concentration during up-

titration was found in the titration from FiO_2 of 0.5 to 1.0 (Table 1). The median (IQR) duration of the FiO_2 to reach the desired concentration at the distal part of the circuit during down-titration was 70.7 (39.9 – 88.8) s. The largest delay in reaching the desired concentration during down-titration was found in the titration from FiO_2 0.8 to 0.5 (Table 1).

With a leak of 50%, up-titration took a median (IQR) duration of 20.0 (17.8 – 28.6) s, with again the largest delay in titration of FiO_2 from 0.5 to 1.0 (Table 1). Down-titration with 50% mask leakage resulted in a median (IQR) duration of 22.1 (20.9 – 28.7) s for the FiO_2 to reach the desired concentration at the distal part of the circuit. The largest delay was found during down-titration of FiO_2 from 0.8 to 0.5 (Table 1).

Table 1 | Duration to achieve desired FiO_2 in bench test

Change in FiO_2	Duration (s) 0% leak n = 6	Duration (s) 50% leak n = 21
Up titration		
FiO_2 0.3-0.5	40.9 ± 10.8	17.9 ± 0.2
FiO_2 0.5-1.0	80.8 ± 17.0	26.6 ± 4.2
Down titration		
FiO_2 1.0-0.8	65.0 ± 19.6	21.1 ± 0.4
FiO_2 0.8-0.5	100.6 ± 10.6	34.6 ± 6.0
FiO_2 0.5-0.3	69.3 ± 2.4	24.5 ± 3.9
FiO_2 0.3-0.21	32.6 ± 8.2	19.7 ± 2.4

Data are presented as mean ± SD

There was a positive association between the duration to achieve the desired FiO_2 at the distal part of the Neopuff™ circuit and the desired FiO_2 difference (longer duration when aiming for a larger FiO_2 difference), the direction of titration (up instead of down) and the occurrence of no leak (R^2 0.863, F 65.016, p<0.001, Table 2).

Table 2 | Multiple linear regression analysis for the association between duration to achieve desired FiO_2 and direction of titration, occurrence of leak and desired FiO_2 difference

Variables	Regression coefficient β (95% CI)	Standardized β	t	P-value
Occurrence of leak[a]	-38.317 (-44.973 – 31.662)	-0.782	-11.743	< 0.001
Direction of titration[b]	-23.973 (-32.540 – 15.405)	-0.464	-5.707	< 0.001
Desired FiO_2 difference	1.220 (0.900 – 1.539)	0.634	7.789	< 0.001

Reference is the occurrence of no leak (a) and titration downwards (b)

Stabilization of infants

Data was recorded from the stabilization of eight preterm infants. Included infants had a median (IQR) gestational age of 29^{+0} (28^{+2} – 30^{+0}) weeks and birth weight of 1290 (1240 – 1488) grams. All except one infant needed PPV during resuscitation. A total of 55 FiO_2 titrations occurred in these infants, with a median (IQR) of 7 (5 – 9) per infant. The median (IQR) desired FiO_2 difference was 0.16 (0.09 – 0.21). Median (IQR) time between titration episodes was 52.5 (27.0 – 103.0) s. In 17/55 (31%) titration episodes, the time until the next titration was less than 30 s.

Overall, there was a variable delay in time to achieve desired FiO_2 at the distal part of the circuit (median (IQR) duration 19.0 (0.0 – 57.0) s). FiO_2 at the distal part of the Neopuff™ circuit changed during titration with a median (IQR) speed of 0.75% (0.42 – 1.28) per s.

There were only four titration episodes in which the average amount of leak was > 50%. We observed a difference in median (IQR) speed with which FiO_2 at the distal part of the Neopuff™ changed: 0.7(0.42 – 1.09) % per s with an average mask leak of 0 – 49 %, compared to 2.47 (0.26 – 3.57) % per s with an average mask leak of > 50 %.

The desired FiO_2 was never reached before the titration of FiO_2 proceeded in 27/55 (49%) of titrations. This was not influenced by the occurrence of mask leakage (no leak: 24/48 (50%) vs leak: 3/7 (43%), p=1.000).

DISCUSSION

This study shows a clear delay in obtaining the desired oxygen concentration at the distal part of the Neopuff™ circuit in both the bench test and during stabilization of preterm infants at birth. As the international resuscitation guideline prescribes evaluation periods of 30 s, the clinical evaluation of the infant and physiological parameters might precede the effect of the performed intervention (e.g. titration of oxygen).(3) This is demonstrated by the finding that in half of all titration episodes, the desired FiO_2 was not yet reached at the distal part of the Neopuff™ circuit. In addition, the time between two titration episodes was less than 30 s in 31 % of titrations performed in this study.

Our results confirm the findings of the study of Follett et al.(14) who observed that the achievement of desired oxygen concentration at a test lung was delayed. However, the titration of oxygen in their study was slightly different than our study, and it is not clear

what the time intervals between titration steps were. Follett et al.(14) also used different ventilators and different lengths of ventilation circuits, while we used the equipment that we use in the clinical setting. However, while both the current trial and the trial of Follett et al.(14) demonstrated that there appears to be a delay in achievement of desired FiO_2, the exact duration of delay might be dependent on multiple variables, including type of ventilator and length of ventilation circuits. In addition, the rate with which the desired FiO_2 is reached in the infant might also be dependent of the volume containing the FiO_2 that needs to be replaced, which is influenced by the pressure administered (PIP and PEEP), respiratory rate and type of respiratory support (CPAP vs PPV vs sustained inflation).

We observed a higher duration to obtain the desired FiO_2 in the bench test, compared to the clinical stabilization procedures. As the desired FiO_2 was not reached in 49 % of all titrations, the duration to obtain the desired FiO_2 was based on the time between titrations and represents an underestimation of the actual duration. Therefore, the delay in obtaining the desired FiO_2 may be closer to the values seen in the bench test.

In addition, the lower duration to reach the desired FiO_2 during stabilization of preterm infants could also be due to the occurrence of leak, as the duration increases when there is no leak. In this study, only 4/55 titration episodes occurred during ventilation with an average of > 50 % leak. One should aim for a minimum level of leakage between the face mask and the face of the infant to achieve adequate ventilation, which, in clinical practice is shown to be difficult to accomplish with a high variability in percentage of leak.(13) These findings indicate that, when ventilating adequately (thus without mask leakage), following an adjustment in FiO_2 there could be a delay in obtaining the desired oxygen concentration at the infant. Furthermore, it is likely that this delay will reduce as the amount of leak increases. However, when mask leakage is variable, it is unclear when the desired oxygen concentration will be reached, possibly leading to over- and under-titration and an increased risk of hypoxia and hyperoxia.

The explanation of the delay in obtaining the desired oxygen concentration is still not clear. We have contacted the manufacturer of the Neopuff™ Infant Resuscitator (Fisher & Paykel Healthcare Auckland, New Zealand), and they acknowledge the results of the study, but the explanation for this delay still remains unclear. They recommend that clinicians should be aware of this when titrating oxygen to achieve target oxygen saturations and allow time for the system to equilibrate. We speculate that the delay might be influenced by not having a continuous flow through the circuit, particularly during inflations. Most T-piece resuscitators like the Neopuff™ have the PIP valve

located inside the box at the proximal end of the circuit and a PEEP valve located at the distal, infant end of the circuit. During an inflation, the PEEP valve is closed (by placing a finger on it) and the circuit, which includes the infants lungs, is pressurized by the flow of gas from the Neopuff™ down the circuit and into the infant. In the absence of leak, once the set PIP pressure is reached, the PIP valve opens and so gas stops flowing down the circuit and instead begins to flow out of the PIP valve, located upstream of the circuit, in the box. As such, during inflations, when the PIP pressure is reached, very little gas will flow down the circuit to the infant, thereby greatly increasing the time for the desired FiO_2 to reach the infant. In case of leak, gas will continue to flow down the circuit, particularly if the set PIP is not reached, thereby reducing the duration to reach the desired FiO_2. During lung deflation, lifting the finger from the PEEP valve allows expired gas from the infant to flow out through the PEEP-valve. In addition, the decrease in pressure allows the PIP valve to close which redirects gas flow down the circuit and out through the PEEP valve. Thus, at end-expiration all gas flowing into the Neopuff™ flows down the ventilation circuit and out the PEEP valve, allowing the set air-oxygen mixture to rapidly reach the distal (infant end) of the circuit.

However, if correct, the variability in time for the desired FiO_2 to reach the infant end of the circuit may be explained by the degree of leak and the relative amount of time spent at either PIP or PEEP.

CONCLUSION

In summary, there is a clear delay in set up of FiO_2 at the proximal part of the T-piece ventilator and achievement of desired FiO_2 at the distal part. This delay is clinically relevant when aiming for adequate mask ventilation, whereby over- and under titration of oxygen might result in an increased risk of hypoxia and hyperoxia.

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