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Clinical paper

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 FiO₂ at the oxygen blender and the desired FiO₂ 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. FiO₂ was titrated following resuscitation guidelines. The duration for the desired FiO₂ to reach either the test lung or face mask was recorded, both with and without leakage. A respiratory function monitor was used to record FiO₂ and amount of leak.

Results: In bench tests, the median (IQR) time taken to achieve a desired FiO₂ was 34.2 (21.8–69.1) s. This duration was positively associated with the desired FiO₂ difference, the direction of titration (upwards) and the occurrence of no leak (R² 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) g), the duration (19.0 (0.0–57.0) s) required to reach a desired FiO₂ was less, but still evident. In 27/55 (49%) titrations, the desired FiO₂ was not achieved before the FiO₂ levels were again changed.

Conclusion: There is a clear delay before a desired FiO₂ 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.

Keywords: FiO₂ titration, Resuscitation, Preterm infant, Respiratory support

Table of contents summary

There is a clear delay in set up of FiO₂ at the proximal part of the T-piece ventilator and achievement of desired FiO₂ at the distal part.

What is known on this subject

During resuscitation of preterm infants at birth, FiO₂ is titrated based on SpO₂, with evaluation every 30 s. However, the time for the gas mixture with the desired oxygen concentration to reach the infant at the distal part of the circuit is still unclear.

What this study adds

There is a clear delay in set up of FiO₂ at the proximal part of the T-piece ventilator and achievement of desired FiO₂ at the distal part. 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 hypoxia and hyperoxia.

Abbreviations: CPAP, Continuous positive airway pressure; FiO₂, Fraction of inspired oxygen; NICU, Neonatal intensive care unit; PEEP, Positive end expiratory pressure; PPV, Positive pressure ventilation; RFM, Respiratory function monitor; SpO₂, Oxygen saturation.

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Introduction

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 drive¹. Most preterm infants need respiratory support after birth to aerate their lungs and gain adequate oxygenation². 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 oxygenation⁵.

During stabilization after birth, additional oxygen needs to be titrated based on recommended oxygen saturations (SpO₂) 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 normograms⁶. To achieve oxygen saturations in this range, neonatal resuscitation guidelines recommend commencing resuscitation with a fraction of inspired oxygen (FiO₂) of 0.21–0.3³. 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 oxygen³. The study of Goos et al. showed that the concentration of oxygen 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 FiO₂⁵.

While the adjustment of FiO₂ 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 FiO₂ 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 FiO₂ at the oxygen blender and the desired FiO₂ reaching the preterm infant during respiratory support at birth.

Methods

An observational study was conducted at the Neonatal Intensive Care Unit (NICU) 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/min, Positive End Expiratory Pressure (PEEP) of 8 cm H₂O, and a Peak Inspiratory Pressure (PIP) of 20 cm H₂O. FiO₂ 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 (Fig. 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, FiO₂ 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 FiO₂ at the test lung was recorded, whereby a margin of 5% difference between FiO₂ 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 uncommon¹³. 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 FiO₂, using the same increments as those used during the bench test: FiO₂ was started at 0.3, and increased to 0.5 and 1.0 if SpO₂ remained below international normograms⁶. In addition, FiO₂ was decreased whenever SpO₂ exceeded 90% to 0.8, 0.5, 0.3 and 0.21. Again, we analysed the time delay between titration of FiO₂ at the proximal part of the circuit and the desired FiO₂ being achieved at the distal part, accepting a 5% difference between those measurements. The amount of leakage was taken into consideration when analysing the results.

In both parts of the study, a RFM was used for recording FiO₂ 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 facemask, thereby calculating inflation pressures, flow and tidal volumes. The difference between inspired and expired tidal volume estimates leak from the facemask, 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 analysers were calibrated at the start of every test and clinical observation.

Data of both parts of the study was analysed using Microsoft Excel (Microsoft Corporation, Washington, United States). During stabilization of infants, FiO₂, SpO₂ and respiratory function were recorded at 0.5 s intervals. Significant leak was accepted as being >50% facemask leak. In the event that titration proceeded before the desired FiO₂ 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 FiO₂.

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 FiO₂, with the difference in FiO₂ that was aimed for during titration and the occurrence of leak,

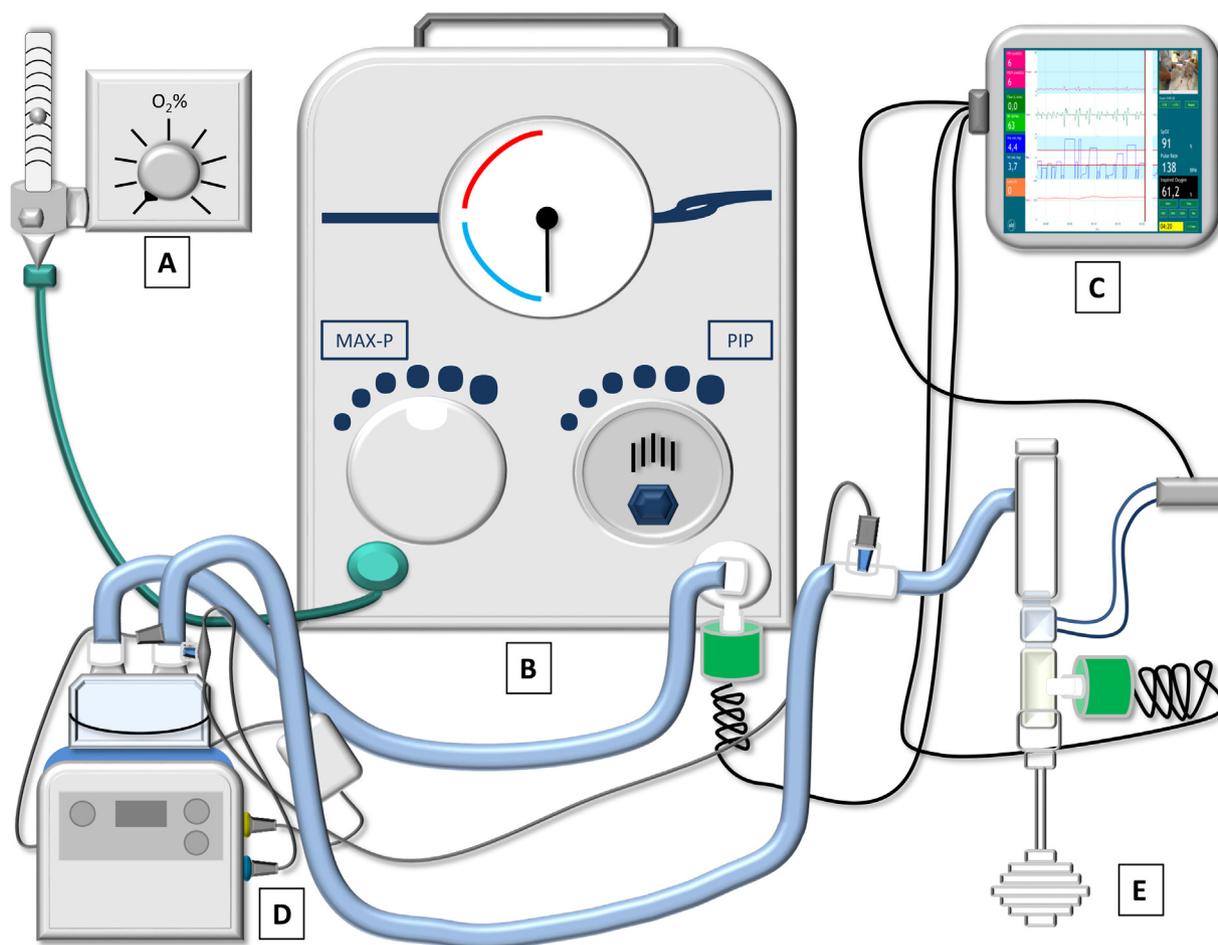


Fig. 1 – Set-up bench test. A: Oxygen blender. B: Neopuff™ T-piece resuscitator. C: Respiratory Function Monitor. D: Humidifier. E: Test lung.

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 analyser at the proximal part of the circuit reached the desired oxygen concentration within 3 ± 1 s, 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).

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).

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) g. 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)

Table 1 – Duration to achieve desired FiO₂ in test situation.

| Change in FiO ₂ | Duration (seconds) 0% leak | N | Duration (seconds) 50% leak | N |
|----------------------------|----------------------------|---|-----------------------------|---|
| Up titration | | | | |
| FiO ₂ 0.3–0.5 | 40.9 ± 10.8 | 6 | 17.9 ± 0.2 | 6 |
| FiO ₂ 0.5–1.0 | 80.8 ± 17.0 | 6 | 26.6 ± 4.2 | 6 |
| Down titration | | | | |
| FiO ₂ 1.0–0.8 | 65.0 ± 19.6 | 6 | 21.1 ± 0.4 | 6 |
| FiO ₂ 0.8–0.5 | 100.6 ± 10.6 | 6 | 34.6 ± 6.0 | 6 |
| FiO ₂ 0.5–0.3 | 69.3 ± 2.4 | 6 | 24.5 ± 3.9 | 6 |
| FiO ₂ 0.3–0.21 | 32.6 ± 8.2 | 6 | 19.7 ± 2.4 | 6 |

Data are presented as mean ± SD.

Table 2 – Multiple linear regression analysis for the association between duration to achieve desired FiO₂ and direction of titration, occurrence of leak and desired FiO₂ difference.

| Variables | Regression coefficient β (95% CI) | Standardized β | t | P-value |
|-------------------------------------|-----------------------------------|----------------|---------|---------|
| Test situation | | | | |
| 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).

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 FiO₂ at the distal part of the circuit (median (IQR) duration 19.0 (0.0–57.0) s). FiO₂ at the distal part of the Neopuff™ circuit changed during titration with a median (IQR) speed of 0.75% (0.42–1.28) per second.

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 FiO₂ at the distal part of the Neopuff™ changed: 0.7% (0.42–1.09) per second with an average mask leak of 0–49%, compared to 2.47% (0.26–3.57) per second with an average mask leak of >50%.

The desired FiO₂ was never reached before the titration of FiO₂ 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 FiO₂ 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. who observed that the achievement of desired oxygen concentration at a

test lung was delayed¹⁴. 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. also used different ventilators and different lengths of ventilation circuits, while we used the equipment that we use in the clinical setting¹⁴. However, while both the current trial and the trial of Follett et al. demonstrated that there appears to be a delay in achievement of desired FiO₂, 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 FiO₂ is reached in the infant might also be dependent of the volume containing the different FiO₂ that needs to be replaced, which is influenced by the pressure administered (peak inspiratory pressure and positive end expiratory pressure), respiratory rate and type of respiratory support (CPAP vs PPV vs sustained inflation).

We observed a higher duration to obtain the desired FiO₂ in the bench test, compared to the clinical stabilization procedures. As the desired FiO₂ was not reached in 49% of all titrations, the duration to obtain the desired FiO₂ was based on the time between titrations and represents an underestimation of the actual duration. Therefore, the delay in obtaining the desired FiO₂ may be closer to the values seen in the bench test.

In addition, the lower duration to reach the desired FiO₂ 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 facemask 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 leak¹³. These findings indicate that, when ventilating adequately (thus without mask leakage), following an adjustment in FiO₂ 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 infant's 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 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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Conflict of interest statement

The authors have no conflicts of interest relevant to this article to disclose.

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