

**Effects of closed-loop automatic control
of the inspiratory fraction of oxygen (FiO₂-C)
on outcome of extremely preterm infants -
a randomized controlled parallel group multicenter trial
for superiority to evaluate safety and efficacy**

FiO₂-C



Conflict of interest statement



- **No conflict of interest in the context of $\text{FiO}_2\text{-C}$**
- The group of Tübingen was involved in the development of the CLAC controller (Leonie-plus).

$\text{FiO}_2\text{-C}$

Frequency and timing of intermittent hypoxemic episodes in ELGAN infants



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DeFiore et al. J. Peds 2010



Association of intermittent hypoxemic episodes with Laser-ROP



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DeFiore et al. J. Peds 2010



Association of intermittent hypoxemic episodes with adverse long-term outcome



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Poets et al. JAMA 2015



Background I: Hypoxemic Episodes



- Preterm infants suffer from intermittent hypoxemic episodes.
- These intermittent hypoxemic episodes are associated with long-term NDI.
- More prolonged episodes and episodes occurring at a later postnatal age seem to be particularly associated with adverse outcome.
- Role of (‘overshoot’-) hyperoxemic episodes is less well studied and remains unclear



The invention of closed-loop FiO_2 -Controllers



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The invention of closed-loop FiO_2 -Controllers



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Background II

Closed-loop automated control of FiO_2 ($\text{FiO}_2\text{-C}$) reduces:

- spontaneous hypoxemic episodes due to respiratory instability
- time in hyperoxemia due to inappropriately high FiO_2

and increases:

- time in SpO_2 target range

Effect of closed-loop automated control of FiO_2 on %-time in SpO_2 -target range



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$\text{FiO}_2\text{-C}$

Poets CF, Franz AR ADC 2016 accepted



Polish contribution to the field of closed-loop automated control of FiO_2



- 2 groups from Poland (Poznan and Warzaw) contributed to the RCT trial published by vanKaam [J Peds 2015]
- The use of CLiO_2 resulted in significantly decreased time with SpO_2 at SpO_2 extremes if compared to ,attentive‘ or ,observative‘ manual adjustments [Wilinska M., Ann Agric Environ Med. 2015]
- M. Wilinska reported ,routine‘ use of CLiO_2 in 121 mechanically ventilated preterm infants for up to 9 days. [Wilinska M., Dev Period Med 2015]

Problems to date



- To date all randomised FiO_2 -C studies have been:
 - a) very short-term
(maximum time on FiO_2 -Controller: 24h)
 - b) cross-over
 - c) outcome variables were %-time in SpO_2 -target range etc.

- No conclusion can be made with regard to:
 - a) effects on longer-term, clinically relevant outcomes
 - b) safety during long-term application (weeks & months), during weaning from FiO_2 and from positive pressure support



Hypothesis

Closed-loop automated control of FiO_2 ($\text{FiO}_2\text{-C}$) will reduce the incidence of:

- Death or
- severe retinopathy of prematurity, or
- bronchopulmonary dysplasia, or
- necrotizing enterocolitis

until discharge from hospital as well as the incidence of:

- Death or
- cognitive or language delay, or
- CP, hearing or visual impairment at 24 months corrected age

- ELGAN infants
- randomly assigned to $\text{FiO}_2\text{-C}$ + manual control or to manual control of FiO_2 only
- within 48h after birth
- until 32 (-36) weeks PMA
(depending on need for CPAP)

- AVEA with CLiO₂ (Carefusion)
- FABIAN with PRICO (Acutronic)
- LEONIE with CLAC (Heinen & Löwenstein)
- SOPHIE with SPOC (Stephan)
- other FiO₂-Controller could also be used

The support of the companies is appreciated!

Concomittant therapy

- SpO₂-target range at the discretion of each center but within the range of 85-95%
- SpO₂-alarms should activate right outside the targets
- Caffeine citrate early (5)-10-(20) mg/kg/d

Recruitment



We aim:

- to involve 40-60 study centers in Europe
- to screen 3350 ELGANs
- to recruit 2340 ELGANs
- to assess at least 2220 ELGANs at discharge within 3 years



Challenges for $\text{FiO}_2\text{-C}$

- Centers use HFNC or Infant-flow-type CPAP early (before the relevant hypoxemic episodes even start)
- Potential Solution:
Accutronic may have a flow generator with Pricco within 1 year

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Summary

- The $\text{FiO}_2\text{-C}$ study presents great challenges but eventually may help to improve the outcome of the preterm infants and also the performance of the $\text{FiO}_2\text{-C}$ devices.
- We would greatly appreciate your contribution / participation in the study !
- Thank you for coming and listening !

