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
Conflict of interest statement

- No conflict of interest in the context of FiO₂-C
- The group of Tübingen was involved in the development of the CLAC controller (Leonie-plus).
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

DeFiore et al. J. Peds 2010

Graph deleted
Association of intermittent hypoxemic episodes with adverse long-term outcome

Poets et al. JAMA 2015

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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$_2$ (FiO$_2$-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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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 FiO₂-C studies have been:

a) very short-term
   (maximum time on FiO₂-Controller: 24h)

b) cross-over

b) outcome variables were %-time in SpO₂-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 FiO2 and from positive pressure support
Hypothesis

Closed-loop automated control of FiO$_2$ (FiO$_2$-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
Design

- ELGAN infants
- randomly assigned to FiO\textsubscript{2}-C + manual control or to manual control of FiO\textsubscript{2} only
- within 48h after birth
- until 32 (-36) weeks PMA (depending on need for CPAP)
FiO$_2$-C

- AVEA with CLiO$_2$ (Carefusion)
- FABIAN with PRICO (Acutronic)
- LEONIE with CLAC (Heinen & Löwenstein)
- SOPHIE with SPOC (Stephan)
- other FiO$_2$-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 FiO₂-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
Summary

- The FiO$_2$-C study presents great challenges but eventually may help to improve the outcome of the preterm infants and also the performance of the FiO$_2$-C devices.

- We would greatly appreciate your contribution / participation in the study!

- Thank you for coming and listening!