PROTOCOL TITLE

Predictive value of the pressure-flow cerebral autoregulatory capacity in the extremely preterm infant during transitional circulation: towards an automatic, reliable, real-time assessment.

SHORT TITLE

CAR in SafeboosC-III.

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1. INTRODUCTION AND RATIONALE

Preterm birth remains an important risk factor for adverse neurological outcome (1). Stabilization of the cardio- and neurovascular system to provide optimal brain perfusion and oxygenation is one of the major goals of neonatal intensive care, to promote growth and optimal development. Impaired cerebral pressure-flow autoregulatory capacity (CAR) is a marker of disease severity and adverse outcome in preterm infants (2, 3, 4, 5, 6, 7, 8, 9, 10).

CAR can be measured continuously by objectivating the co-incidence of spontaneous mean blood pressure oscillations and near-infrared spectroscopy (NIRS) measured cerebral tissue oxygenation (rStO2). CAR monitoring is feasible in the neonatal population but to date, there is no clinical gold standard methodology for CAR assessment (11, 12). The ultimate goal is to use cotside CAR continuous assessment to individualize treatment in the unstable sick infant.

CAR can be studied using the inversely proportional parameter transfer function (TF) gain (11). TF gain is a frequency-domain method that quantifies the damping effect between the input (blood pressure) and the output ($rStO_2$) in coherent epochs (with passive-pressure cerebral circulation) and is expressed as % $rStO_2$ change/mmHg mean blood pressure (MBP) change. TF gain as a measure for CAR is studied in small patient cohorts (13, 14, 15).

A bivariate autoregressive coherence method (BiAR-COH) to explore CAR has been proposed by Riera et al. (3). The main difference respect to the TF gain is that BiAR-COH demands both temporal and frequency dependence (time-frequency domain method). The same authors introduced the partial directed coherence (PDC) method to address the condition of directionality (2). That means, the system will only consider those events in which changes in MBP induce changes in $rStO_2$.

The SafeboosC-III study investigated the benefit of treatment guided by cerebral oximetry monitoring for the first three days after birth compared to routine care in a large cohort of extremely preterm infants. Death or severe brain injury defined by cranial ultrasound at 36 weeks postmenstrual age was the

primary composite outcome (16). The 2 year follow-up study is currently ongoing (https://clinicaltrials.gov/ct2/show/NCT05134116).

The aim of this study is to use this large detailed SafeboosC dataset with a structured outcome to validate TF gain, BiAR-COH and PDC methods as CAR parameters. Furthermore, we aim to investigate study reproducibility and inter-method comparisons with regards to their predictive capacity for adverse outcome. Finally, we aim to explore whether treatment guided by cerebral oximetry influences the infant's CAR capacity.

We hypothesize that infants with abnormal outcome will have impaired CAR capacity according to the different autoregulation estimators and more prolonged periods of impaired CAR capacity during transitional circulation (2, 3, 13).

2. OBJECTIVES

Primary objectives

- To assess the ability of the three CAR classifiers to predict survival without severe neurological complications at 36 weeks postmenstrual age.
- To validate the predictive capacity of three estimators of CAR capacity (TF gain, BiAR-COH and $PDC_{MBP>>rStO2}$) to define disease progression and vulnerability to brain injury.

Secondary objectives

- To study the effect of different artifact reduction methods to promote real-time CAR assessment.
- To refine the analytical method to increase the strength of BiAR-COH, $PDC_{MBP>>rStO2}$ and TF gain classifiers in the clinical setting.
- To study the use of artificial intelligence to define the best CAR approach.

Exploratory objectives

- To evaluate if treatment guided by cerebral oximetry influences CAR capacity.

3. STUDY DESIGN

Ancillary SafeboosC-III study

4. STUDY POPULATION

4.1 Population

Infants born with a gestational age below 28 week enrolled in the SafeBoosC-III trial.

4.2 Inclusion criteria

Infants of SafeboosC-III randomised to rStO2 monitoring or control group with blinded NIRS recording. Availability of continuous rStO2, SaO2 and MBP data with sample frequency of 1/30 Hz or higher in the first 72 hours after birth.

4.3 Exclusion criteria

Mortality in first 72 hours of life.

Withdrawal from SafeboosC-III study protocol.

4.4 Sample size calculation

A post-hoc sample size calculation will be done based on the number of eligible patients.

5. TREATMENT OF SUBJECTS

Not applicable (retrospective chart review study).

6. INVESTIGATIONAL PRODUCT

Not applicable (retrospective chart review study).

7. NON-INVESTIGATIONAL PRODUCT

Not applicable (retrospective chart review study).

8. METHODS

8.1 Study endpoints

Primary endpoints:

- Proportion of neonates surviving without severe neurological complications* at 36 weeks postmenstrual age in newborns who had good CAR (determined by TF gain, BiAR-COH and $PDC_{MABP>>rStO2}$) compared to neonates with impaired CAR.

  *Defined by cranial ultrasound (cUS) as: cerebral haemorrhage grade III or IV, cystic periventricular leukomalacia, post-haemorrhagic ventricular dilatation, cerebellar haemorrhage or cerebral atrophy.

- Area under the receiver operating characteristic (ROC) curve (AUC) to evaluate the predictive capacity (for the various outcomes of interest) of the three CAR estimators.

Secondary endpoints:

- Autonomy (automatic window selection) and improved precision
- To study the effect of artefact reduction on clinical data.
- To study AI approaches.

8.2 Analytical approach to the CAR methods

To measure CAR, $rStO_2$ is a valid surrogate for CBF under the assumption of stable SaO_2 and constant cerebral metabolism (17). Real-time, simultaneous, time-locked data acquisition system for the physiological parameters MBP, SaO2 and rStO2 is used.

8.2.1 TF gain

Oblique subspace projections will be used to eliminate the contribution of SaO_2 in the $rScO_2$ signal (18). CAR will be studied using the inversely proportional parameter TF gain. TF gain values will be explored in overlapping 20-min epochs (overlap of 19 min) with significant coherence (COH) between (SaO_2-corrected) $rScO_2$ and MBP in the very-low-frequency (VLF) range, which indicates that CAR is pressure passive (19). TF gain quantifies the damping effect between the input (MBP) and the output (SaO_2-corrected $rStO_2$) and is expressed as % $rStO_2$ change/mmHg MBP change. A higher TF gain indicates that moderate changes in MBP are associated with larger changes in CBF, reflecting decreased CAR (20). Significant COH will be tested using Monte Carlo simulations (21). Signal detrending and Welch's method (overlapping 10-min subwindows) will be used to reduce edge effects and noise, respectively. Analysis will be performed using MATLAB (The Mathworks, Natick, MA).

8.2.2 BiAR-COH and PDC

The principle behind BiAR-COH (3) is that each sample of signal X can be predicted using the past samples of a given signal. If the inclusion of the past observations of another signal Y improve the prediction of X, that means the two signals are related. This can be expressed as a bivariate autoregressive model (BiAR). The number of past samples to be considered is automatically calculated using the Akaike information criterion (22) and the Bayesian information criterion (23) taking the lowest value (between 3 and 25 samples).

To derive the frequency domain interpretation of the BiAR, the coherence analysis is applied to the BiAR coefficients, leading to the BiAR-COH, using the Fourier transform over the frequency bands of 0.003-0.04 Hz.

The partial directed coherence (PDC) method (24) considers the synchronicity and directionality of signal dependence across frequencies. With respect to synchronicity, the PDC method only takes into account the changes in signals that are closely related in time. In terms of directionality, the PDC method identifies the source of changes, i.e., the changes in signal B

that are the physical consequence of changes in signal A (25). Accordingly, the PDC method returns all potential combinations between signals: $PDC_{MBP>>rStO2}$ and $PDC_{rStO2>>MBP}$.

For BiAR-COH and PDC analyses disruption-free zones are automatically segmented into non-overlapping 30-min epochs if SaO_2 was stable (less than 5% variation). Each epoch is filtered with a linear high order low-pass FIR filter at 0.095 Hz and resampled at 0.2 Hz. The mean of the signal is subtracted. Epochs that satisfied the conditions of stationarity (covariance stationarity) and that have at least 3% variation are selected for analyses. An in-house Matlab toolbox (The MathWorks, Inc., Natick, MA, US) enables the selection of epochs. Stationarity is tested using the ADF and KPSS tests (26, 27) which are applied separately for the MBP and rStO2 epoch waveforms.

8.3 Other study variables

- Time and hour of birth
- Treatment with inotropes in first 3 days after birth
- Gestational age
- Birth weight
- Type of oximeter and sensor
- CUS diagnosis (early: day 4-7, at 36 weeks post-menstrual age)
- Main neonatal diagnoses (death before 36 weeks, bronchopulmonary dysplasia, necrotising enterocolitis, early onset sepsis, late onset sepsis, severe retinopathy of prematurity with need for treatment)

9. SAFETY REPORTING

Not applicable (retrospective chart review study).

10. STATISTICAL ANALYSIS

10.1 Primary Endpoint:

- **TF gain**

A multivariate linear model for longitudinal measures with an unstructured covariance matrix will be used to compare the evolution of study parameters between groups over time. A direct likelihood approach will be adopted such that cases with missing information were still included in the analysis. Least-squares means (and their 95% confidence interval (CI)) are reported. *P* values are given after Bonferroni Holm correction for multiple testing. Relation with outcome will be assessed using univariable and bivariate logistic regression models.

Furthermore, using all available individual 20-min epoch data for each infant, linear mixed models with (correlated) random intercepts and slopes on (log-transformed) TF gain and $rStO_2$ values will be used comparing the relation TF gain-MBP and $rStO_2$-MBP as a function of outcome. Restricted cubic splines with four knots will be used to allow a nonlinear relation between the pairs. The model contains terms for the spline basis (2 extra terms on top of the intercept and the linear slope), the main effect of group (i.e. the levels of the outcome) and additional terms referring to the interaction between group and MBP. The result is given of an overall test for any difference between both levels in the relation. Predicted mean outcomes will be plotted with pointwise 95% confidence intervals. Empirical standard errors will be used to correct for misspecification of the covariance structure. Analyses will be performed on the information from the first three days separately. Gestational age will be added as a continuous covariate in the model. A *P* value < .05 is considered statistically significant. All reported *P* values are two-sided.

- **BiAR-COH and PDC**

Receiver operating characteristic (ROC) curves are used to analyze the predictive capacity of the CAR estimators (BiAR-COH and $PDC_{MBP>>rStO2}$ and $PDC_{rStO2>>MBP}$) on clinical outcomes per epoch (adjusted and unadjusted by gestational age). The CAR threshold is calculated using the maximum value of Youden's index. To quantify the effect of the CAR estimators on patient outcome, generalized estimating equations are used to adjust the effect of repeated measures (multiple epochs) in a given patient, adjusted by gestational age. Accordingly, pBiAR-COH and $pPDC_{MBP>>rStO2}$ and $pPDC_{rStO2>>MBP}$ are defined as the averaged epoch prediction values per patient. The quantitative data are given as means (±SD) and the qualitative data as counts and percentages.

10.2 Secondary and explorative endpoints

Defined by engineers.

11. ETHICAL CONSIDERATIONS

Amendment on the SafeboosC-III protocol in the participating centres.

12. ADMINISTRATIVE ASPECTS

Data transfer between centres to Leuven will be possible by a secure link by https://www.liquidfiles.com/. A link for data delivery will be provided by the study team in Leuven.

13. STRUCTURED RISK ANALYSIS

Not applicable (retrospective chart review study).

14. REFERENCES

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