

STUDY TITLE

Breathing Pattern Variability in Preterm Infants: Effect of Non-invasive Neurally Adjusted Ventilatory Assist (NAVA-NIV) Versus Nasal Intermittent Positive Pressure Ventilation (PC-NIV), a Cross-Over Study.

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STUDY OBJECTIVES

Primary: To evaluate the effect of NAVA-NIV compared to Nasal Intermittent Positive Pressure Ventilation (PC-NIV) at the same of peak inspiratory pressure in terms of breath-by-breath variability of tidal breathing amplitude in preterm infants < 37+0 weeks+days post-menstrual age.

Secondary: To evaluate the effect of NAVA-NIV compared to Nasal Intermittent Positive Pressure Ventilation (PC-NIV) at the same level of peak inspiratory pressure in terms of variability of the other breathing pattern parameters; lung mechanics; gas exchange; rate of apneic episodes; bradycardia and desaturations; respiratory asynchrony and comfort.

STUDY DESIGN

It will be a monocentric, randomized, cross-over trial.

The setting will be the Neonatal Intensive Care Unit (NICU) of Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, in collaboration with the Laboratorio di Tecnologie Biomediche – TBMLab, Dipartimento di Elettronica, Informazione e Bioingegneria – DEIB, Politecnico di Milano University, Milan, Italy.

STUDY POPULATION

Preterm infants born < 37 weeks of gestation, requiring non-invasive respiratory support

INCLUSION CRITERIA

- Preterm birth < 37 weeks of gestational age
- Need of non-invasive respiratory support
- Parental consent

EXCLUSION CRITERIA

- Major congenital abnormalities of the cardio-respiratory systems
- Severe Respiratory Failure requiring intubation and mechanical ventilation at the time of the study; pH < 7.25 pCO₂> 65 mmHg; pulmonary hypertension requiring pharmacological treatment (Nitric Oxide, Sildenafil)
- Hypoxic-Ischaemic Encephalopathy, neurological disorders which may compromise the integrity of the neural transmission from the brain to the diaphragm
- Contraindication to orogastric tube insertion (e.g. oesophageal atresia, gastric perforation...)
- Haemodynamic instability requiring inotropic agents
- Any condition that would expose the patient to undue risk as deemed by the attending physician

STUDY INTERVENTION

Preterm infants matching the inclusion criteria (listed elsewhere) will be enrolled in a cross-over trial of two modes of non-invasive respiratory support: nasal intermittent positive pressure ventilation (PC-NIV) and NAVA NIV (Sevo-n Neonatal Ventilator, Getinge, Solna, Sweden).

In order to compare the two modes at the same level of PIP, a 20-minute registration of ventilator parameters during assistance on NAVA-NIV will allow calculating the mean PIP (peak inspiratory pressure).

The ventilator settings other than PIP (i.e. FiO₂, PEEP, IT, RR) will be based on the setting optimized by the attending physicians prior to the study entry.

Infants will then receive a randomized sequence of 1-hour assistance by NAVA NIV and 1-hour assistance PC-NIV at the same level of PIP or vice-versa.

FiO₂ will be adjusted in order to maintain SpO₂ 88-93% in infants ≤ 32 weeks of postconceptional age, 90-95% in infants > 32 weeks of postconceptional age.

Infants will receive respiratory support in a standardized supine position during the study period.

RANDOMIZATION

The randomization will be created by generating casual numbers by specific MatLab functions. Closed, opaque, sequentially numbered envelopes will be then created by the collaborators from the department of Elettronica, Informazione e Bioingegneria – DEIB, Politecnico di Milano University. After enrolment, physicians will open the envelop containing the sequence of randomization.

ENDPOINTS

PRIMARY

Breath-by-breath variability of tidal breathing amplitude.

Tidal breathing amplitude will be recorded continuously via two, high resolution, small cameras placed inside the infant's incubator and skin (non-invasive) markers. Ventilator parameters (flow, pressure, volume and electrical diaphragmatic activity) will be recorded continuously during the study. Data will be analysed *a posteriori* applying parametric or non-parametric statistical tools depending on the results of normal distribution test and long term correlation properties will be studied by the DFA (Detrended Fluctuation Analysis) technique or similar.

SECONDARY

Breathing pattern variability (Tidal Volume, Respiratory Rate, Inspiratory Time, Duty Cycle)

Ventilator parameters (flow, pressure, volume and the electrical diaphragmatic activity) will be recorded continuously during the study, chest and abdominal volume displacement will be detected by two high-resolution camera--based 3D depth sensors placed in the incubators. The variability of the breathing pattern will be then analyzed by the DFA technique.

Lung mechanics (lung reactance and lung resistance)

Lung mechanics will be measured by mean of the Forced Oscillation Technique (FOT) at the end of each step, by superimposing to the ventilator waveform an oscillatory pressure of small amplitude and high frequency (Fabian, Acutronic Medical Systems AG, Switzerland). Flow and pressure signals will be collected and respiratory mechanics will be evaluated by estimating offline the total respiratory system input impedance and expressed as reactance and resistance.

Gas exchange

Fraction on inspired oxygen (FiO₂), SpO₂ and transcutaneous pCO₂ will be monitored continuously.

Rate of apnoeas, desaturations, bradycardias

Episodes of apnoea, desaturation, and bradycardia will be recorded over each study period

Rate of patient-ventilator asynchronies

Patient-ventilator asynchronies will be calculated by continuous recording of ventilator parameters (flow, pressure, volume and electrical diaphragmatic activity) and by continuous recording of abdominal and chest movements by high resolution cameras placed in the incubators and skin markers on abdomen and chest

Patient's comfort

Patient's comfort will be assessed by the attending nurse at the end of each step by means of the COMFORT scale at the end of each step.

Number of caregiver interventions required

The number of interventions required by the attending personnel during each step will be also recorded: for instance interventions to improve comfort, to adjust the ventilator interface, to optimize the efficacy of respiratory support, suctioning ...

STUDY DURATION/TIME POINTS

The first part of the study will be to determine the mean PIP during NAVA NIV over a 20-minute period, followed by the cross-over, made up of two steps lasting 1 hour each. At the end of each step, a 5-minute measurement by FOT will take place. Data will be assessed at the beginning of the study (t₀), every 10 minutes during the first 30 minutes and every 5 minutes during the last 30 minutes.

STATISTICAL ANALYSIS

The sample size of the study was calculated by G-power. 25 patients are needed for a two-tailed power > 0.80 with $\alpha=0.05$, hypothesizing a normal distribution and an effect dimension of 0.59. The effect dimension was calculated considering a correlation among groups = 0.5 and tidal volume variations (used as a quantitative index for characterizing breathing amplitude variations) of newborn infants supported by nasal CPAP (0.79 ± 0.14) and after the application of nasal CPAP at 2 cmH₂O (0.71 ± 0.13) [Zannin, *Pediatr Pulmunology* 2018].

Measured Variables and Data Analysis

From the flow, pressure, volume and electrical diaphragmatic activity tracings, the breathing patterns will be measured (see above). The end-expiration will be identified by the two small, high resolution camera-based 3D sensors and the skin markers. FiO₂, SpO₂, tc pCO₂ will be also measured. At the end of each step lung resistance (Rrs) and reactance (Xrs) will be assessed by FOT. A dedicated

operator will record the number of episodes of apnea, bradycardia and desaturation. Patient's comfort will be assessed by the COMFORT scale. Mean (or median as appropriate) and SD (or IQR) will be calculated for all the parameters measured. Short-term variability will be determined by the variation coefficient (SD). Long-term correlation will be evaluated by the DFA technique. ANOVA or Friedman test for repeated measurements as appropriate according to data distribution will be used to verify differences in each of the parameters analysed, considering groups.

ETHICS

The present study will be conducted following the ICH/GCP International Conference of Harmonization/Good Clinical Practice rules and all the applicable regulations, including the declaration of Helsinki, June 1964, modified by the World Medical Association General Assembly in Seoul, 2008.

The study protocol has been approved by the local Ethical Committee, Comitato Etico Milano di Area 2, on March 1st 2019.

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