Nasal High Frequency Oscillation Ventilation(NHFOV) vs. Nasal Continuous Positive Airway Pressure(NCPAP) vs Nasal Intermittent Positive Pressure Ventilation （NIPPV）as Post-extubation Respiratory Support in Preterm Infants With Respiratory Distress Syndrome:a Multicenter Randomized Controlled Trial

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1.Trial design

This was a multi-center, three-arms, parallel, randomized, controlled trial with a superiority design, conducted in China. Since safety data will also be analyzed it may be considered a phase II/III trial. Since the trial will enroll all eligible patients irrespective of their lung mechanics/physiopathology and eligibility will be judged on the basis of simple clinical data commonly used in daily NICU care, it may be considered as pragmatic trial. In fact, no particular entry criteria or diagnostic procedure will be required to enroll patients; no biological samples will be collected and no additional measures will be taken. Conversely, since subgroup analyses will be performed on patients defined *a posteriori* according to their actual lung physiopathology, they should be considered explanatory subgroup (preliminary) analyses. Results of subgroup analyses will anyway need confirmation in future, specifically designed trials. A total of 69 NICUs are included in this trial. All these NICUs belong to 30 provinces or cities or autonomous regions of Chinese mainland (apart from Tibet which has been excluded for the high altitude). The trial has been designed with the collaboration of an European investigator expert in NHFOV (DLD) and the Data Monitoring Board is also composed by independent international experts.

2. Study aim and Hypothesis

Our aim is to verify the hypothesis that NHFOV is more efficacious than CPAP or NIPPV to reduce the need for IMV in neonates born between 25 and 32 weeks' gestation, after their first extubation and until their final NICU discharge.

3. Inclusion criteria

For a neonate to be included 4 criteria must be fulfilled: **(1)** gestational age (GA) between 25+0 and 32+6 weeks (estimated on the postmenstrual date and early gestation ultrasonographic

findings); **(2)** assisted with any type of endotracheal ventilation; **(3)** post-conceptional age < 36 weeks; **(4)** ready to be extubated for the first time (extubation readiness requires fulfilling of all the following criteria: **a.** having received at least one loading dose of 20 mg/kg and 5 mg/kg daily maintenance dose of caffeine citrate; **b.** pH>7.20 and $PaCO_2 \leq 60$ mmHg (these may be evaluated by arterialized capillary blood gas analysis or appropriately calibrated transcutaneous monitors. Venous blood gas analysis cannot be used); **c.** Paw of 7-8 or 8-9 cmH_2O, in conventional and oscillatory ventilation, respectively; [6] **d.** $FiO_2 \leq 0.30$; **e.** sufficient spontaneous breathing effort, as per clinical evaluation)

4. Exclusion criteria

Neonates who never needed intubation and IMV are not eligible for the study; similarly, a neonate randomized but never extubated is not eligible in the study. Moreover, neonates with at least one of the following criteria are also not eligible: (1) major congenital anomalies or chromosomal abnormalities; (2) neuromuscular diseases; (3) upper respiratory tract abnormalities; (4) need for surgery known before the the first extubation; (5) Grade IV-intraventricular hemorrhage (IVH) occurring before the first extubation; (6) birth weight <600 g; (7) congenital lung diseases or malformations or pulmonary hypoplasia.

5. Randomization

Neonates will be randomized and assigned either to CPAP, NIPPV or NHFOV arms with a 1:1:1 ratio, when patients fulfil all inclusion criteria and extubation is deemed imminent (anyway within 1h). Randomization cannot be done earlier. Simple randomization will be done according to a computer-generated random number table and will be posted in a specific secured website 24/7 available. Twins will be allocated in the same treatment group. Infants randomized to one

arm cannot crossover to the other or vice-versa during the study. Patients will remain under the assigned respiratory support until the weaning criteria will be met. In case of intubation, when the baby will be extubated, he will receive again his original treatment according to randomization.

6. Primary outcomes

The primary outcomes will be: **(1)** duration of IMV (in days); **(2)** ventilator-free days ; **(3)** the number of reintubation. Neonates will be re-intubated if one of the following occurs:

a. severe respiratory acidosis (defined as $PaCO_2$>65 mmHg with pH<7.2);

b. hypoxia refractory to study intervention (defined as SpO_2<90%, with FiO_2=0.4 and maximal pressures allowed in the study arm – see below) for at least 4h;

c. severe apnea (defined as recurrent apnea with >3 episodes/h associated with heart rate <100/min or a single episode of apnea requiring bag and mask ventilation, or associated with SpO_2<85% and FiO_2>0.6);

d. pulmonary hemorrhage (defined as brightly blood tracheal secretion associated with sharp increase in oxygen and Paw and with the occurrence of “white lungs”, new infiltrates or consolidations at the chest X-rays or lung ultrasound);

e. severe respiratory distress (defined as Silverman score >4) for at least 4h;

f. hemodynamic instability, defined as mean arterial pressure <10 th percentile of appropriate nomograms or anyway need of dopamine (if >5 γ/Kg/min) or dobutamine (if >5 γ/Kg/min) or any dose of noradrenaline, adrenaline, milrinone, nitric oxide or other pulmonary vasodilators.

g. cardio-respiratory arrest.

7. Secondary outcomes

The secondary outcomes will be: ////////////////////////////////////(1) airleaks occurring after the study intervention; (2) BPD; (3) hemodynamically significant patent ductus arteriosus (PDA); (4) retinopathy of prematurity (ROP) > 2nd stage; (5) necrotizing enterocolitis (NEC) ≥2nd stage; (6) IVH >2nd grade; (7) need for postnatal steroids; (8) in-hospital mortality; (9) composite mortality/BPD; (10) weekly weight gain (in grams/days) for the first 4 weeks of life or until NICU discharge, whichever comes first; (11) weekly number of apneas; (12) nasal skin injury; (13) Premature Infant Pain Profile (PIPP) score in the first 48 hours from the onset of study intervention.

8. ***Samplesize calculation***

It is difficult to calculate a sample size, since this is the first trial to investigate NCPAP vs NIPPV vs NHFOV in post-extubation phase in preterm babies. However, a previous prospective, cohort, non-randomized, pilot study comparing post-extubation NIPPV and NHFOV in preterm neonates provided data about the primary outcome "duration of mechanical ventilation". This preliminary study showed a reduction of ≈30% for babies receiving NHFOV, as compared to those treated with NIPPV, but it has been presented only as abstract so far. A randomized trial of NIPPV vs CPAP by Ramanathan et al. showed a similar reduction. Since these trials have not the same design of ours, we decide to be more prudent and we aimed a difference of 20% in the duration of mechanical ventilation. Considering an alpha-error of 0.05 (with a Bonferroni correction at 0.017) and a power of 95%, 480 neonates should be enrolled in each arm (with a 1:1:1 design). Thus, a total of at least

1440 neonates should be enrolled.

9. ***Data collection***

All data can be obtained from the clinical notes. Data will be recorded in real time on web-based case report forms provided by OpenCDMS. The website will be tested with fictitious data before the actual enrolment. Data will be entered by an assessor per each center. Assessors will be research nurses or local investigators blinded to the study intervention and not involved in patients' care. Access to the form will be secured and patients will be de-identified. Clinical information will be collected at the following time-points:

1. Before the intervention begins: information on eligibility; baseline clinical informations, respiratory diagnosis, critical risk index for babies-II (CRIB-II) score.

2. Following study intervention: ventilatory parameters, SpO_2, blood gas values before the extubation if available. PaO_2, $PaCO_2$, SpO_2 and pH between 6h and 24h from the extubation.

3. Follow-up: NICU length stay, duration of IMV, number of reintubation, ventilator free days, duration of oxygen therapy, duration of the study intervention (CPAP, NIPPV or NHFOV), airleaks, PDA, BPD, ROP >2nd stage, NEC≥2nd stage, IVH>2nd grade, need for postnatal steroids, in-hospital mortality, composite mortality/BPD, weekly weight gain (in grams/d) for the first 4 weeks of life or until NICU discharge, whichever comes first. Moreover, the following safety data will be recorded: weekly number of vomiting/d, weekly volume of gastric residual (ml/d); weekly number of apneas/d; nasal skin injury (weekly defined by a 1-2-3 clinical score). These outcomes will be averaged over each week for the first 4 weeks of life or until NICU discharge, whichever comes first. Finally, PIPP score will be recorded in the first 48h from the allocation. Abdominal circumference at 48h and 96h from the instigation of CPAP, NIPPV or NHFOV will also be

recorded.

10. ***Statistics***

An external safety and efficacy monitoring conducted a formal interim analyse at 50% of the enrolment. The study team was not informed of interim results. The final analysis was conducted at the end of the study only after all efficacy data were complete and finalized.

The primary and secondary outcomes were analyzed on an intention-to-treat basis. For the primary outcome and dichotomous secondary outcomes, we calculated a risk difference (with a two-sided 95% confidence interval) in percentage points between treatment groups. We used chi-square tests to compare dichotomous outcomes and the appropriate parametric test (one-way ANOVA) or Mann-Whitney *U* test (Hodges-Lehmann median difference) to compare continuous outcomes. *P* values < 0.05 will be considered statistically significant. All analyses were carried out with computer software (SPSS 16.0 for Windows; IBM).

11. ***Data Monitoring Board***

The Data Monitoring Board analyzed all data in an *interim* analysis at 50% of the trial enrolment. The board was composed by one epidemiologist, three international neonatologists or pediatric intensivists experts in respiratory care.

1、Dr. Dezhi Mu, Professor of Pediatrics, West China Second University Hospital, Sichuan University, Chengdu, Sichuan.

2、Dr. Mingyan Hei, Professor of Neonatal Centre, Beijing Children's Hospital , Capital Medical University, Beijing National Centre for Children's Health, Beijing,

China.

3、Dr. Lyv Deliang, Shenzhen Centre for chronic disease control. Dr. Lyv Deliang served as a consultant for the statistical analyse