1 **Protocol title:**

2 **Noninvasive high frequency oscillation**

3 **ventilation (NHFOV) *vs* continuous positive**

4 **airway pressure (CPAP) *vs* noninvasive**

5 **positive pressure ventilation (NIPPV) as**

6 **post-extubation respiratory support in**

7 **preterm neonates: a multicenter**

8 **randomized trial.**

9

10 **Protocol identifying number: Clinical Trials.gov NCT02570217**

11 **Local number: N.3.0 (last version)/ date: Nov 15/2017**

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BACKGROUND

Respiratory distress syndrome (RDS) is the main cause of respiratory failure in preterm neonates, its incidence varying from ≈80% to ≈25% depending on gestational age.[1] When optimal prenatal care is provided, the best approach to treat RDS, according to several recent trials,[2,3] consists in providing continuous positive airway pressure (CPAP) from the first minutes of life using short binasal prongs or masks,[4,5] followed by early selective surfactant administration for babies with worsening oxygenation and/or increasing work of breathing. Any effort should be done to minimize the time under invasive mechanical ventilation (IMV).[6] Nonetheless, clinical trials have shown that a relevant proportion of preterm neonates fails this approach and eventually need IMV.[7,8,9] The duration of IMV is a well known risk factor for the development of broncho-pulmonary dysplasia (BPD) - a condition associated with significant morbidity and mortality.[10,11]

To minimize the duration of IMV, various non invasive respiratory support modalities are available in neonatal intensive care units (NICU). CPAP is presently the most common technique used in this regard. However, a systematic review has shown that non-invasive positive pressure ventilation (NIPPV) reduces the need for IMV (within one week from extubation) more effectively than NCPAP, although it is not clear if NIPPV may reduce need for intubation longterm and it seems to have no effect on BPD and mortality.[12] NIPPV main drawback is the

50 lack of synchronization, which is difficult to be accurately achieved and

51 is usually unavailable. A more recent alternative technique is

52 non-invasive high frequency oscillatory ventilation (NHFOV) which

53 consists on the application of a bias flow generating a continuous

54 distending positive pressure with oscillations superimposed on

55 spontaneous tidal breathing with no need for synchronization. The

56 physiological, biological and clinical details about NHFOV have been

57 described elsewhere.[13]

58 To date, there is only one small observational uncontrolled study

59 about the use of NHFOV after extubation in preterm infants.[14] Other

60 relatively small case series or retrospective cohort studies suggested

61 safety, feasibility and possible usefulness of NHFOV and have been

62 reviewed elsewhere.[13] The only randomized trial published so far

63 compared NHFOV to biphasic CPAP, in babies failing CPAP[15] and it

64 has been criticized for methodological flaws and for not taking into

65 account respiratory physiology.[16] An European survey showed that,

66 despite the absence of large randomized clinical trials, NHFOV is quite

67 widely used, at least in some Countries and no major side effects are

68 reported, although large data about NHFOV safety are lacking.[17] This

69 may be due to the relative NHFOV easiness of use but evidence-based

70 and physiology-driven data are warranted about this technique.

71 NHFOV should theoretically provide the advantages of invasive

72 high frequency oscillatory ventilation (no need for synchronization, high

73   efficiency in CO_2 removal, less volume/barotrauma) and nasal CPAP

74   (non-invasive interface, oxygenation improvement by the increase in

75   functional residual capacity through alveolar recruitment). NHFOV

76   should allow to increase mean airway pressure (Paw) avoiding gas

77   trapping and hypercarbia, thanks to the superimposed high frequency

78   oscillations. Therefore, NHFOV is more likely to be beneficial for those

79   neonates requiring high distending pressure to open up their lungs,

80   such as babies at high risk of extubation failure due to severity of their

81   lung disease. This may also be the case of extremely preterm,

82   BPD-developing neonates who have increased airway resistances,

83   while they are subjected to a deranged alveolarization and lung growth.

84   Neonates presenting with respiratory acidosis may also benefit from

85   NHFOV. Several animal and bench studies investigated the physiology

86   and peculiarities of NHFOV[13] and these data should be used to

87   conduct a physiology-guided trial in order to avoid errors done in the

88   early trials about invasive high frequency ventilation.[16]

89   This study will be the first large trial aiming to compare CPAP *vs*

90   NIPPV *vs* NHFOV in preterm neonates after surfactant replacement

91   and during their entire NICU stay, to reduce the total need of invasive

92   ventilation. Since there is a lack of formal data regarding NHFOV safety,

93   some safety outcomes will also be considered. Specific subgroup

94   analysis will be conducted for pre-specified groups of patients who may

95   most likely benefit from NHFOV, according to the above-described

96   physiological characteristics.

97

98   **OBJECTIVES**

99   To test whether NHFOV is more efficacious than CPAP or NIPPV,

100   as post-extubation respiratory support, to reduce the need for IMV all

101   along their NICU stay in neonates born between 25 and 32-weeks'

102   gestation.

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METHODS

1.Trial design

This will be a **blinded, 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 NICU daily care, it may be considered a **pragmatic** trial.[18] Conversely, since subgroup analyses will be performed on patients defined according to their actual lung physiopathology, they should be considered **explanatory subgroup analyses**.[18] Results of subgroup analyses will anyway need confirmation in future, specifically designed trials.   A total of 69 NICUs are included in this trial (**Fig.1 and appendix**). All these NICUs belong to 30 provinces or cities or autonomous regions of Chinese mainland (apart from Tibet which has been excluded for the too high altitude). The trial has been designed with the collaboration of international investigators experts in NHFOV and noninvasive respiratory support composing the international advisory board.

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137 **Figure 1. Neonatal Intensive Care Units participating to the trial.**

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140 *2. Inclusion criteria*

141   For a neonate to be included three criteria must be fulfilled: **(1)**

142 gestational age (GA) between 25+0 and 32+6 weeks (estimated on the

143 postmenstrual date and early gestation ultrasonographic findings) and

144 post-conceptional age <36 weeks; **(2)** assisted with any type of

145 endotracheal ventilation; **(3)** ready to be extubated for the first time

146 (extubation readiness requires fulfilling of all the following criteria: **a.**

147 Having received at least one loading dose of 20 mg/kg and 5 mg/kg

148 daily maintenance dose of caffeine citrate; **b.** pH>7.20 $PaCO_2$ ≤60

149 mmHg (these may be evaluated by arterialized capillary blood gas

150 analysis or appropriately calibrated transcutaneous monitors[19] – see

151 appendix. <u>Venous blood gas values cannot be used</u>); **c.** Paw ≤7-9

152   cmH_2O;[6] **d.** $FiO_2 \leq 0.30$; **e.** sufficient spontaneous breathing effort, as

153   per clinical evaluation[20]).

154

155   ***3. Exclusion criteria***

156   Neonates who never needed intubation and IMV are not eligible

157   for the study; similarly, a neonate randomized but never extubated is

158   not eligible in the study. Moreover, neonates with at least one of the

159   following criteria are also not eligible: (1) major congenital anomalies or

160   chromosomal abnormalities; (2) neuromuscular diseases; (3) upper

161   respiratory tract abnormalities; (4) need for surgery known before the

162   the first extubation; (5) Grade IV-intraventricular haemorrhage (IVH)

163   occurring before the first extubation;[21] (6) congenital lung diseases or

164   malformations or pulmonary hypoplasia; (7) birth weight <600 grams.

165   ***4. Randomization***

166   **Neonates will be randomized and assigned either to CPAP,**

167   **NIPPV or NHFOV arms with a 1:1:1 ratio, when patients fulfil all**

168   **inclusion criteria and extubation is deemed imminent (anyway**

169   **within 1h). <u>Randomization cannot be done earlier.</u>** Simple

170   randomization will be done according to a computer-generated random

171   number table and will be posted in a specific secured website available

172   on 24/7. Twins will all be allocated in the same treatment group.

173   **Infants randomized to one arm cannot crossover to the other or**

174   **vice-versa during the study. Patients will remain under the**

175 **assigned respiratory support until the weaning criteria (see below)**

176 **will be met. In case of intubation, when the baby will be extubated,**

177 **he will receive again his original treatment according to**

178 **randomization**. This can be summarized by **Fig.2.**

179

180 **Figure 2. Study design.** Neonates will stay on the assigned

181 intervention up to the final weaning. No cross-over allowed. In case of

182 intubation, when the baby will be extubated, he will receive again his

183 original treatment according to randomization.

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186 *5. Blinding*

187 Blinding towards the caregivers is impossible and blinding

188 towards the patients makes no sense. **However, outcomes'**

189 **assessors will be blinded, as endpoints will be recorded by**

190 **investigators not involved in patients' care. An assessor per each**

191 **participating NICU will be nominated. Moreover, investigators**

performing the final statistical analyses will be blinded to the

treatment allocation, as data collected by assessors will be

inserted in the dedicated website and the arms' allocation will be

re-coded.

6. Primary outcomes

The primary outcomes will be: **(1) duration of IMV (in days); (2)**

ventilator-free days (calculated as described in the appendix); **(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 apnoea (defined as recurrent apnoea with >3 episodes/h

associated with heart rate <100/min or a single episode of apnoea

requiring bag and mask ventilation, or associated with $SpO_2<85\%$ and

$FiO_2>0.6$);

d. pulmonary haemorrhage (defined as brightly blood tracheal

secretion associated with sharp increase in oxygen and Paw

requirement and with occurrence of "white lungs", new infiltrates or

consolidations at the chest X-rays);

215 **e.** severe respiratory distress (defined as Silverman score >4) for at

216 least 4h;

217 **f.** haemodynamic instability, defined as mean arterial pressure <10th

218 percentile of appropriate nomograms[22;23] or anyway need of dopamine

219 (if >5 γ/Kg/min) or dobutamine (if >5 γ/Kg/min) or any dose of

220 noradrenaline, adrenaline, milrinone, nitric oxide or other pulmonary

221 vasodilators.

222 **g.** cardio-respiratory arrest.

223 *7. Secondary outcomes*

224 The secondary outcomes will be: **(1) airleaks** (pneumothorax

225 and/or pneumomediastinum) occurred *after* the extubation; **(2) BPD**,

226 defined according to the NICHD definition (more details in the

227 appendix);[24] **(3) haemodynamically significant patent *ductus***

228 ***arteriosus* (PDA),** defined according to local NICU protocols; **(4)**

229 **retinopathy of prematurity (ROP) > 2nd stage;[25] (5) necrotizing**

230 **enterocolitis (NEC) ≥ 2nd stage;[26] (6) IVH>2nd grade;[21] (7) need for**

231 **postnatal steroids; (8) in-hospital mortality**; **(9) composite**

232 **mortality/BPD; (10) Weekly weight gain (in grams/day) for the first**

233 **4 weeks of life or until NICU discharge, whichever comes first.**

234 *8. Safety outcomes*

235 The safety outcomes will be the following: **(1) weekly number of**

236 **vomiting** per day; **(2) weekly volume of gastric residual** (ml/day); **(3)**

237 **weekly number of apnoeas** per day; **(4) nasal skin injury** (weekly

238   defined by a clinical score[27] as: 0 (zero, absence of injury), stage I

239   (non-blanching erythema), stage II (superficial erosion), stage III

240   (necrosis of full thickness of skin) – more details in the appendix).

241   **These outcomes will be averaged over each week for the first 4**

242   **weeks of life or until NICU discharge, whichever comes first.**

243   Finally, **(5) Premature Infant Pain Profile score[28]** will be considered

244   (averaged from values available in the first 48h from the allocation to

245   CPAP, NIPPV or NHFOV).

246   *9. Standard protocol approvals, registrations, and patient*

247   *consents*

248   The study was approved by the Ethics Committee of Daping

249   Hospital (n.201721) and registered in the clinicaltrial.gov registry (ID:

250   NCT03181958). The trial was performed in accordance with the

251   approved guidelines and regulations of the participating institutions.

252   Informed consent will be obtained antenatally or upon NICU admission

253   from parents or guardians.

254   *10. Study Intervention*

255   When the neonate had fulfilled the extubation criteria, this latter will

256   took place with a gentle intratracheal suction, following local policies.

257   Upper airways will then be suctioned and intervention will be started

258   immediately as follows:

259   **10.1 Ventilators**

260   - **CPAP**: CPAP will be provided by either variable flow or continuous

261 flow devices, as there is no evidence that one type of CPAP

262 generator would be better than any other.[29]

263 - **NIPPV**: NIPPV will be provided by any type of neonatal ventilator.

264 Synchronization will not be applied, as many currently marketed

265 neonatal ventilators usually do not provide it for NIPPV.[30]

266 - **NHFOV**: NHFOV will only be provided with piston/membrane

267 oscillators able to provide a real oscillatory pressure with active

268 expiratory phase (that is, Acutronic FABIAN-III, SLE 5000,

269 Loweinstein Med LEONI+, Sensormedics 3100A). Other machines

270 providing high frequency ventilations will not be used.

271 Before the beginning of the study all ventilators will be checked to

272 ensure that there is no malfunction.

273 **10.2 Interfaces**

274 CPAP, NIPPV and NHFOV will be all administered through short,

275 low-resistance binasal prongs and/or nasal masks, since these are

276 supposed to be the best in terms of resistive charge, leaks and/of

277 comfort.[4,5] Nasal prongs size will be chosen according to the nares'

278 diameter as the best fitting ones (the largest ones that fit the nares

279 without blanching the surrounding tissues) and following

280 manufacturer's recommendations. Nasal masks will also be

281 appropriately sized according to manufacturer's recommendations.

282 Alternating masks and prongs, according to clinical evaluation, is

283 allowed in order to reduce the risk for nasal skin injury. Particular care

284 (e.g.: pacifiers, positioning, nursing) will be applied to reduce leaks and

285 improve patients' comfort. These latters will be evaluated through a

286 dedicated 30 min observation period when study intervention will be

287 instigated. Non pharmacological sedation with pacifier and 33%

288 glucose solution will be provided, when needed; no other sedation will

289 be allowed. RAMCannula® are not allowed in the trial due to their

290 resistive charge and their relevant pressure leaks.[31,32]

291 **10.3 Ventilatory management**

292 The three different respiratory supports will be managed as follows:

293 - **CPAP**: Neonates assigned to the CPAP group were initiated on a

294 pressure of 5 cmH_2O. CPAP can be raised in steps of 1 cmH_2O up

295 to 8 cmH_2O. If this is not enough to maintain SpO_2 between 90%

296 and 95%, FiO_2 will be added up to 0.40.

297 - **NIPPV**: neonates assigned to the NIPPV group will be started with

298 the following parameters: **a)** positive end-expiratory pressure

299 (PEEP) of 4 cmH_2O (can be raised in steps of 1 cmH_2O to max 8

300 cmH_2O, according to the oxygenation). **b)** Peak Inspiratory

301 Pressure (PIP) of 15 cmH_2O (can be raised in steps of 1 cmH_2O to

302 max 25 cmH_2O, according to oxygenation, $PaCO_2$ levels and the

303 chest expansion); maximal allowed FiO_2 will be 0.40 and SpO_2

304 targets will be 90-95%. **c)** inspiratory time (IT) will be 0.45 – 0.5 sec

305 (according to clinicians' evaluation of leaks and the appearance of

306 the pressure curve: a small pressure plateau is required and flow

307   may be set accordingly) and rate will be started at 30 bpm (can be

308   raised in steps of 5 bpm to max 50 bpm, according to $PaCO_2$

309   levels).

310   - **NHFOV**: neonates assigned to NHFOV will be started with the

311   following boundaries:

312   **a)** Paw of 10 cmH_2O (can be changed in steps of 1 cmH_2O within

313   the range range 5-

314   16 cmH_2O); Paw will be titrated (within the range) according to open

315   lung strategy, performing alveolar recruitment, similar to what is done in

316   endotracheal high frequency oscillatory ventilation (see **Fig.3**) targeting

317   a $FiO_2 \leq 25$-30%.[33] Maximal allowed FiO_2 will be 0.40 and SpO_2 targets

318   will be 90%-95%. **b)** frequency of 10Hz (can be changed in steps of

319   1Hz within the range 8-12Hz). **c)** Inspiratory time 50% (1:1).[34] **d)**

320   amplitude 25 cmH_2O (can be changed in steps of 5 cmH_2O within the

321   range 25-50 cmH_2O);[34,35] amplitude will be titrated according to $PaCO_2$.

322   It is not strictly necessary to have visible chest oscillations, as $PaCO_2$

323   elimination during NHFOV also occurs in the upper airway dead

324   space.[36] In case of hypercarbia, amplitude will be increased first and

325   then frequency will be lowered (within the above-described ranges),

326   however, if nasal masks are used amplitude should be kept at the

327   maximum and $PaCO_2$ controlled by frequency titration, as the CO_2

328   elimination using nasal masks seems inferior.[37]
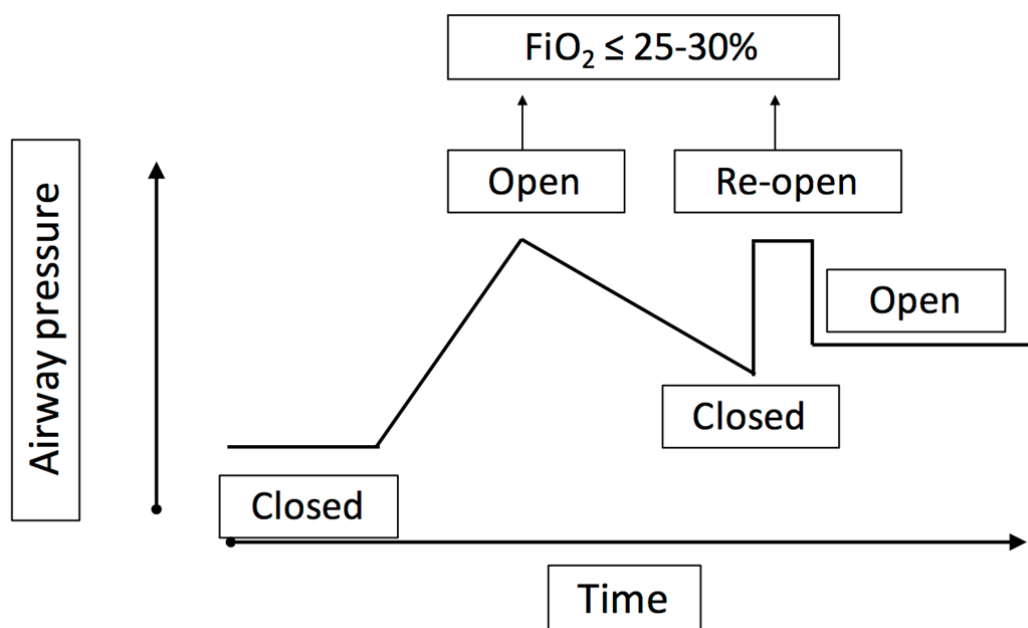
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332   **Figure 3. Alveolar recruitment according to the open lung strategy,**

333   **as described in[33].** This should be followed in NHFOV arm, and

334   repeated as per clinical need within the suggested mean airway

335   pressure boundaries (5-16 cmH$_2$O, with changes in steps of 1 cmH$_2$O).

336   [*Courtesy of Prof. A. van Kaam and Prof. D. De Luca*].

337

338

339   **10.4 Monitoring and concurrent treatments/diagnostic**

340   **measures**

341   PaCO$_2$ will be monitored using arterialized capillary blood gas analysis

342   and/or transcutaneous monitors according to local policies.

343   Transcutaneous monitoring will be performed according to the

344   American Association of Respiratory Care guidelines[19] and the

345   manufacturer's recommendations. Frequency of blood gas analysis will

346   be decided by the attending clinicians. All neonates will be continuously

347   monitored for SpO_2, ECG, heart and respiratory rate. To avoid

348   abdominal distention, a feeding tube will be placed in the stomach

349   through the mouth and gas will periodically aspirated according to

350   nurses' evaluation in all study arms.

351   Moreover, the following treatments or tests will be provided:

352   • Heart ultrasound to evaluate cardiac morphology, pulmonary

353   pressures and PDA, within the first 3 days of life and subsequently

354   repeated, if needed.

355   • Cerebral ultrasound within 48 hours of life and weekly thereafter,

356   until discharge, if needed.

357   • Routine measures to prevent BPD; routine fluid/nutritional policy;

358   routine caffeine therapy.

359   • Placement of umbilical central venous catheter and/or peripherally

360   inserted central venous lines. Placement of arterial lines if needed,

361   according to local policies.

362   • Routine therapies according to local policies (i.e.: antibiotics, PDA

363   closure drugs…).

364   In general, routine clinical assistance and nursing will not be

365   changed because of the study, out of the trial intervention; the clinical

366   assistance will be identical in the three study arms. No additional blood

367   samples are required for this study.

368

369   **10.5 Weaning from study interventions**

370   The study intervention will be progressively weaned, according to

371   clinical evaluation and respecting the following guidelines:

372   o in the CPAP arm, pressure will be reduced by 1 cmH$_2$O steps down

373   to a minimum of 3 cmH$_2$O;

374   o in the NIPPV arm, PIP and PEEP will be reduced by 1 cmH$_2$O steps

375   down to a minimum of 3 and 5 cmH$_2$O, respectively. Similarly,

376   frequency will be reduced to a minimum level of 20 bpm in steps of 5

377   bpm.

378   o in the NHFOV arm, amplitude will be reduced to the minimum initial

379   level of 20 cmH$_2$O and Paw will be reduced by 1 cmH$_2$O down to a

380   minimum of 3 cmH$_2$O.

381   The study intervention (CPAP, NIPPV or NHFOV) will be stopped

382   when the above-described minimum parameters are reached and

383   maintained for at least 48h with the following: (1) FiO$_2$ ≤0.25; (2)

384   Silverman score <3; (3) no apnoeas or bradycardia without

385   spontaneous recovery. If a baby will desaturate (SpO$_2$ <85% with

386   FiO$_2$>25%) or has relevant dyspnoea (Silverman≧3) or more than 3

387   apnoeas/day the intervention (CPAP, NIPPV or NHFOV) will be

388   restarted for at least 48h and then re-evaluated. The end of study

389   intervention may occur at any time during hospitalization if the above

390   described criteria are met. When study interventions end, the neonate

391   may be placed under low flow oxygen therapy (max 1 L/min), if needed,

392   according to clinicians' evaluation and local policies. Anyway, when a

393   post-conceptional age of 36 weeks is reached, if the patient still needs

394   noninvasive respiratory support, he/she will be shifted to CPAP and

395   managed according to clinical evaluation and local policies.

396   ***11. End of the study***

397   A patient may exit from the study for any of the following reasons:

398   1. Death.

399   2. In any case, when the 36 weeks' post-conceptional age is reached.

400   3. If parents or guardians withdraw an already given consent for the

401   participation (in that case the patient will keep receiving the whole

402   routine clinical assistance; data acquired up to that point will be

403   immediately destroyed).

404   ***12. Sample size calculation***

405   It is difficult to calculate a sample size, since this is the first to

406   investigate CPAP *vs* NIPPV *vs* NHFOV in post-extubation phase in

407   preterm babies. However, a previous prospective, cohort,

408   non-randomized, pilot study comparing post-extubation NIPPV and

409   NHFOV in preterm neonates provides data about the primary outcome

410   "duration of mechanical ventilation". This study showed a reduction of

411   ≈30% for babies receiving NHFOV, as compared to those treated with

412   NIPPV.[38]A randomized trial of NIPPV vs CPAP by Ramanathan et al.

413   showed a similar reduction.[39] Since these trials have not the same

414   design of ours, we decide to be more prudent and we aimed a

415   difference of 20% in the duration of mechanical ventilation. Considering

416   an alpha-error of 0.05 (with a Bonferroni correction at 0.017) and a

417   power of 95%, 480 neonates should be enrolled in each arm (with a

418   1:1:1 design). Thus, a total of at least 1440 neonates will be enrolled.

419   Sample size calculation has been performed with GPower 3.1.9.3.[40]

420   **13. Data collection**

421   All data for trial analysis are routine clinical items that can be

422   obtained from the clinical notes. Data will be recorded in real time

423   (every day) on web-based case report forms provided by OpenCDMS.

424   The website will be tested with fictitious data before the actual

425   enrolment. Data will be entered by an assessor per each center.

426   Assessors will be research nurses or local investigators blinded to the

427   study intervention, as they are not involved in patients' care. Access to

428   the form will be password protected and participants will be identified

429   by trial number only. Clinical information will be collected at the

430   following time-points:

431   **Before the intervention begins:** information on eligibility;

432   baseline clinical informations, respiratory diagnosis, critical risk index

433   for babies-II (CRIB-II) score.[41]

434   **Following study intervention:** ventilator parameters, SpO_2, blood

435   gas values before the extubation if available (it is suitable to have at least

436   transcutaneous blood gas values). PaO_2, $PaCO_2$, SpO_2 and pH between

437 6h and 24h from the extubation.

438 **Follow-up:** NICU length stay, duration of IMV, number of

439 reintubation, ventilator free days, duration of oxygen therapy, duration of

440 the study intervention (CPAP, NIPPV or NHFOV), airleaks, PDA, BPD,

441 ROP >2nd stage, NEC≥2nd stage, IVH>2nd grade, need for postnatal

442 steroids, in-hospital mortality, composite mortality/BPD, weekly weight

443 gain (in grams/day) for the first 4 weeks of life or until NICU discharge,

444 whichever comes first. Moreover, the following safety data will be

445 recorded: weekly number of vomiting per day, weekly volume of gastric

446 residual (ml/day); weekly number of apnoeas per day; nasal skin injury

447 (weekly defined by a 1-2-3 clinical score[24] – more details in the appendix).

448 These outcomes will be averaged over each week for the first 4 weeks of

449 life or until NICU discharge, whichever comes first. Finally, the Premature

450 Infant Pain Profile score[25] recorded in the first 48h from the allocation will

451 be recorded. Abdominal circumference at 48h and 96h from the

452 instigation of CPAP, NIPPV or NHFOV will also be recorded.

453 *14. Statistics*

454 Data analysis will be performed blindly to the type of treatment

455 received. An *intention-to-treat* analysis will be applied. An *interim*

456 analysis will be performed at 50% of the enrolment. First, data will be

457 checked for normality using Kolmogorov-Smirnov test and results will be

458 presented as odds ratio (OR) and 95% confidence interval (CI) or

459 adjusted OR and 95%CI, and mean ± standard deviation or median

460 (quartiles), as appropriate. ANOVA and Mann-Whitney test will be

461 applied, according to data distribution. Proportions will be tested using

462 Chi^2 or Fisher tests, as appropriate.

463 If required, according to type of variable and their distributions,

464 logistic or linear regressions will be performed. Multivariate regressions

465 will also be performed for selected outcomes if needed (that is, if a

466 baseline characteristic of the enrolled population differs between the two

467 arms with a $p<0.2$ at the univariate analysis, then the results will be

468 adjusted for that variable). In that case analysis of multicollinearity will be

469 previously performed considering condition index of Eigenvalues and

470 variables inserted in the model will have to carry a Variance Inflation

471 Factor <2.[42,43] p-values <0.05 will be considered statistically significant.

472 The following sub-group analysis will be performed:

473- **1.** Subgroup analysis for **babies ≤28 weeks' gestation**.

474- **2.** Subgroup analysis for **babies who have been invasively ventilated**

475 **for at least 1 week from birth.**

476- **3.** Subgroup analysis for babies with **PaCO$_2$>50mmHg before the**

477 **extubation or at the 6h or 24h after extubation**.

478 *15. Data Monitoring Board (DMB)*

479 Dr. Dezhi Mu, Professor of Pediatrics, West China Second University

480 Hospital, Sichuan University, Chengdu, Sichuan.

481 Dr. Mingyan Hei, Professor of Neonatal Centre, Beijing Children's

482 Hospital, Capital Medical University, Beijing National Centre for

483   Children's Health, Beijing, China.

484   Dr. Lyv Deliang, Shenzhen Centre for chronic disease control.

485   Dr. Lyv Deliang served as a consultant for the statistical analyse

486   ***16. International advisory panel***

487   International colleagues were consulted for the protocol preparation, the

488   training on trialed respiratory support techniques and technical problems that

489   may arise during the study. They will also be able to analyze data in the *interim*

490   analysis at approximately 50% of the trial enrolment. The panel will

491   be composed by international neonatologists or pediatric intensivists experts in

492   respiratory care. This is unusual in a trial about neonatal ventilation but will

493   help to increase the quality of data. The board will advice the principal

494   investigator (YS) who will remain the only complete responsible for any aspect

495   of the trial.

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ETHICAL CONSIDERATIONS

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500   This trial is worth to be conducted given the uncertainty about the effectiveness

501   of the different respiratory support techniques tested. Moreover, NHFOV might

502   be actually superior to the other techniques, as we may hypothesize from the

503   currently available data. In detail, many different types of noninvasive

504   respiratory support are now available and we do not know yet which is the best

505   policy to be applied especially in the babies at highest risk, (i.e.: in those

506   developing BPD). NHFOV has been already studied in preliminary cross-over

507   trials, in bench and animal studies,[13] while invasive HFOV is routinely used for

508   severe respiratory failure worldwide. NIPPV has been studied in several

509   randomized controlled trials enrolling smaller population and/or without triple

510   comparison against CPAP and NHFOV. Thus, there is actually a great drive

511   towards non-invasive ventilation, especially for preterm neonates, and this

512   study is a new step within this framework.

513   Thus, the risks for babies are minimized and the monitoring will report quickly

514   any problem, if any. Out of the studied intervention, the participation to the

515   study will not change in any way the routine clinical assistance set for every

516   patient. Data will be recorded anonymously and will be secured and accessible

517   only to the investigators and to the parents/guardians of the enrolled patients.

518   Data of a specific patient will be immediately destroyed if an already given

519   consent is withdrawn. In no case the recorded data will be used for purposes

520   out of those specified in the trial protocol. Moreover, the trial is only funded by a

521   public Chinese research program, thus it will not have external industrial

522 influences and has the merit to try filling the lack of public funding for neonatal

523 ventilation trials.[44]

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APPENDIX

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A1. CLARIFICATIONS FOR 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. This means that, if a randomized neonate is not actually extubated within 1 hour because there has been a worsening of his conditions or death, he is excluded the study. **Randomization must be done as close as possible to the extubation, once all inclusion criteria are fulfilled (see above), and anyway within 1h from the actual extubation.**

1. **Some exclusion criteria are represented by congenital disorders: when a patient is affected by these disorders his biology and physiology are significantly changed and are not eligible for the study and will not be randomized. If the condition has been discovered/suspected after the randomization but before the study inclusion (that is, before extubation), they will not receive the study intervention and will not entry in the study. If one of these conditions is diagnosed after the inclusion in the study, the neonate will be excluded *a posteriori*.** This is the case of neonates with major congenital anomalies, chromosomal abnormalities, neuromuscular diseases, congenital upper respiratory tract abnormalities and congenital lung diseases or malformations or hypoplasia. Examples of these conditions are: genetic syndromes, surfactant protein

558   defects, congenital adenomatous pulmonary malformations,

559   congenital diaphragmatic hernia or sequestration, congenital

560   hypoventilation syndrome, pulmonary hypoplasia or any metabolic

561   disease.

562   2. **Same applies for the need for surgery anticipated antenatally**

563   **or before the first extubation, as this is usually related to**

564   **congenital malformations. These neonates are not eligible for**

565   **the study and will not be randomized. If the condition has been**

566   **discovered/suspected after the randomization but before the**

567   **study inclusion (that is, before extubation) they will not receive**

568   **the study intervention and will not entry in the study. If a**

569   **surgery will be needed later during the NICU hospitalization for**

570   **other reasons (for instance for PDA ligation or NEC), the**

571   **patient will regularly continue the trial.** Conditions needing

572   surgery will be noticed in the web-based database.

573   3. **Grade IV-IVH known before the first extubation is a significant**

574   **risk factor for prognosis and for quality of life. Continuing the**

575   **NICU care in this situation may be considered unethical,**

576   **depending to different local settings, cultures, ethical and**

577   **religious beliefs. This may significantly impact on the trial**

578   **outcomes. These neonates are not eligible for the study and**

579   **will not be randomized. If grade IV-IVH has been**

580   **discovered/suspected after the randomization but before the**

581   **study inclusion (that is, before extubation), they will not**

582   **receive the study intervention and will not entry in the study.** If

583   Grade IV-IVH will be diagnosed after the study inclusion, the patient

584   will continue the study regularly and this will be noticed amongst the

585   outcomes.

586 **A2. LIST OF STUDY DEFINITION/ASSESSMENTS (IN**

587 **ALPHABETICAL ORDER)**

588 -   **Antenatal steroids.** Antenatal steroid prophylaxis will be

589   considered complete if two 12 mg-doses of betamethasone 24h

590   apart and between 1 day and 7 days before the delivery had been
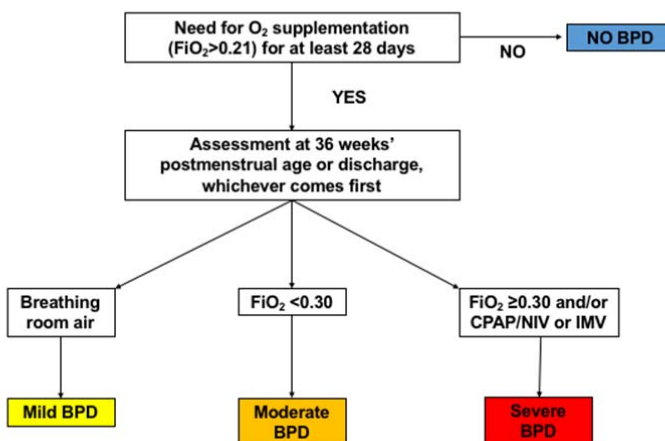
591   given.

592 -   **Blood gas analysis.** Blood gas values may only be obtained in

593   following three ways (<u>venous blood gas analysis is not allowed in</u>

594   <u>the study</u>).

595 ***Arterial blood from indwelling arterial lines,*** if one of these was

596 placed for clinical reasons. As these are likely to be unavailable in the

597 majority of cases, the following two alternative techniques may be

598 used.

599 ***Arterialized capillary blood*** gas analysis is performed, warming a

600 patient's heel for 10 minutes and collecting 200 µL of blood into a

601 heparinized micro-tube. This must be analyzed by a blood gas analyzer

602 within 5 minutes. Blood gas analysis will be obtained upon attending

603 neonatologist decision.

604 ***Transcutaneous blood gas monitoring*** will be performed according

605 to American Associations of Respiratory Care guidelines[19] and the

606 device manufacturer's recommendations and using an electrode

607 temperature of 44 °C for a short time (max 10-15min). Particular care

608 must be provided to avoid skin injury in extremely preterm neonates: in

609 some cases, a temperature of 42°C may be more suitable.

610   -   **BPD definition as per NICHD definition (for neonates ≤32**

611   **weeks' gestation)[24]**

612

613   -   **Clinical Risk Index for Babies (CRIB-II) score.[41]** This is an

614   estimator of the clinical severity at the NICU admission. CRIB-II

615   score considers 4 variables: *birth weight, GA, base excess within*

616   *the 1st hour of life and temperature at the admission* (see below as

617   reproduced from [41])). An online calculator is available at

618   www.sfar.org/scores2/crib22.php

Clinical risk index for babies II (CRIB II) score

619

620   -   **Time on CPAP/NIPPV/NHFOV.** Number of days spent under these

621   respiratory supports will be registered and rounded to the closest

622   entire number.

623   -   **Gestational age (GA).** GA is determined based on sure dates of

624   last menstrual period or early ultrasound scan (within the first

625   trimester). If a discrepancy of more than 2 weeks exists, the early

626   ultrasound scan will be chosen.

627   -   **Nasal injuries.** These are classified by using a clinical score[26] as

628   stage I (non-blanching erythema), stage II (superficial erosion),

629   stage III (necrosis of full thickness of skin) in the skin area in contact

630   with nasal prongs (see below, as reproduced from[27]). <u>The score will</u>

631   <u>be 0 (zero), in case of absence of any injury.</u>

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643   -   **Premature Infant Pain Profile (PIPP) score.[28] (see below,**

644   **reproduced from [28])**

Table V – Premature Infant Pain Profile (PIPP)

Indicators	0	1	2	3
GA in weeks	≥ 36 weeks	32 to 35 weeks and 6 days	28 to 31 weeks and 6 days	< 28 weeks
Observe the NB for 15sec				
Alertness	Active Awake Opened eyes Facial movements present	Quiet Awake Opened eyes No facial movements	Active Sleep Closed eyes Facial movements present	Quiet Sleeping Closed eyes No facial movements
Record HR and SpO_2				
Maximal HR	↑ 0 to 4 bpm	↑ 5 to 14 bpm	↑ 15 to 24 bpm	↑ ≥ 25 bpm
Minimal Saturation	↓ 0 to 2.4%	↓ 2.5 to 4.9%	↓ 5 to 7.4%	↓ ≥ 7.5%
Observe NB for 30 sec				
Frowned forehead	Absent	Minimal	Moderate	Maximal
Eyes squeezed	Absent	Minimal	Moderate	Maximal
Nasolabial furrow	Absent	Minimal	Moderate	Maximal

Absent is defined as 0 to 9% of the observation time; minimal, 10% to 39% of the time; moderate, 40% to 69% of the time; and maximal as 70% or more of the observation time. In this scale, scores vary from zero to 21 points. Scores equal or lower than 6 indicate absence of pain or minimal pain; scores above 12 indicate the presence of moderate to severe pain.
GA – Gestational Age. NB – Newborn.

645

646   -   **Pulmonary hypoplasia.** This will be clinically defined if anamnestic

647   (prenatal findings: small lung volume), imaging (diffuse chest x-ray

648   opacity or hypo-density) and clinical data (extremely low gestational

649   age, olygo-anhydramnios, severe pulmonary hypertension) are

650   present. Pulmonary hypoplasia usually does not allow survival.

651   -   **Respiratory main diagnosis. A respiratory main diagnosis that**

652   **required IMV (± surfactant administration) has to be given**

653   **according to the following criteria. RDS:** respiratory distress

654   appearing within the first 24 h of life, with complete, sustained, and

655   prompt response to surfactant or lung recruitment or both;

656   additional non-mandatory criteria are lung imaging (chest X-rays or

657   ultrasound, according to local policies) supporting the diagnosis or

658   lamellar body counts ≤30 000/mm³, or both.[45]**Pneumonia**:

659   broncho-alveolar lavage fluid or blood positive culture or C-reactive

660   protein and/or procalcitonin beyond the normal values, together with

radiological signs of infection (infiltrates and/or consolidation and/or loss of aeration).[46] **Sepsis (international pediatric sepsis definition)**: presence of systemic inflammatory response syndrome (SIRS) together with a suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection.[47] Evidence of SIRS is given by the presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocytes:

- Core temperature >38.5°C or <36°C.
- Tachycardia, defined as a mean heart >180 bpm in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR bradycardia, defined as a mean heart rate <100 bpm in the absence of external vagal stimulus, -blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.
- Mean respiratory rate >60/min or need for IMV for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed or 10% immature neutrophils.

Evidence of infection includes positive findings on anamnesis, clinical exam, imaging, or laboratory tests.[48] **Meconium aspiration syndrome (MAS):** presence meconium-stained amniotic fluid and secretions upon tracheal suctioning with onset of respiratory distress early from birth

687 and chest X-rays or lung ultrasound typical for MAS.[48] **Neonatal ARDS:**

688 defined as per the international Montreux definition.[45]

689 - **Ventilator free days (VFD)** defined as the number of days spent in

690 the NICU without IMV. One point is given for each day during the

691 NICU stay that patients are both alive and free of mechanical

692 ventilation; as death, is the worst outcome a dead patient is given

693 zero VFD.[49]

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A3. LIST OF DATA TO BE COLLECTED IN THE ELECTRONIC CRF

704

Basic patients' data

705

1. Sex (male/female).

706

2. Gestational age (weeks without decimals).

707

3. Birth Weight (g).

708

4. CRIB-II score[41] at the NICU admission (as described above or

709

through the online calculator cited above).

710

5. Day of age at the first extubation (d).

711

6. Delivery type (Vaginal birth/Elective caesarean delivery/Emergency

712

caesarean delivery).

713

7. Complete Antenatal steroids (yes/no – as defined above).

714

8. Apgar score at 1 and 5 min.

715

9. Surfactant given: (yes/no and which type of surfactant).

716

10. Surfactant dose (mg/kg).

717

11. Number of surfactant doses, if any (1,2,3).

718

12. Mean airway pressure (Paw) at the extubation (cmH_2O).

719

13. FiO_2 and SpO_2 before extubation (% - right before extubation).

720

14. PaO_2 before extubation (mmHg – obtained as described above

721

from the closest available measurement).

722

15. $PaCO_2$ before extubation (mmHg – obtained as described above

723

from the closest available measurement).

724

16. pH before extubation (if available, obtained as described above

725

from the closest available measurement).

726

727 17. Lactate before extubation (if available, obtained as described

728 above from the closest available measurement).

729 18. Type of ventilation at the extubation (Conventional/HFOV).

730 19. Main early respiratory diagnosis

731 (RDS/Pneumonia/Sepsis/ARDS/MAS…).

732 20. Main reason for re-intubation (if any).

733 **Outcomes**

734 1. Extubation failure at 48h (yes/no).

735 2. Paw (cmH_2O), PaO_2 (mmHg), $PaCO_2$ (mmHg) and FiO_2 (%) between

736 6 and 24h after extubation.

737 3. Duration of invasive ventilation (d).

738 4. Ventilator free-days (calculated as described above).

739 5. Number of re-intubations during the NICU stay (total number).

740 6. Duration of treatment (CPAP, NIPPV or NHFOV – d).

741 7. Duration of oxygen treatment (d).

742 8. Need for postnatal steroids (yes/no).

743 9. In-hospital mortality (yes/no).

744 10. Weekly weight gain (g/d) (averaged over each week for the first 4

745 weeks of life or until NICU discharge, whichever comes first, as

746 described above).

747 11. Air leaks after the extubation (yes/no).

748 12. BPD[23] (no/mild/moderate/severe – as described above).

749 13. haemodynamically significant PDA (diagnosed according to local

750   NICU protocols).

751   14. ROP >2nd stage.

752   15. NEC ≥2nd stage.

753   16. IVH >2nd grade.

754   17. NICU length of stay (d).

755   18. Weekly number of vomiting per day (averaged over each week for

756   the first 4 weeks of life or until NICU discharge, whichever comes first,

757   as described above).

758   19. Weekly volume of gastric residual (ml/d) (averaged over each week

759   for the first 4 weeks of life or until NICU discharge, whichever comes

760   first, as described above).

761   20. Weekly number of apnoeas per day (averaged over each week for

762   the first 4 weeks of life or until NICU discharge, whichever comes first,

763   as described above).

764   21. Premature Infant Pain Profile score (averaged from the values

765   available in the first 48h from the allocation, as described above).

766   22. Nasal skin injury (weekly defined by a 0-1-2-3 clinical score, as

767   described above).

768   23. Abdominal circumference (cm) at 48h and 96h after study

769   intervention.

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