



HAL
open science

Nasal High-Frequency Ventilation

Daniele de Luca, Roberta Centorrino

► **To cite this version:**

Daniele de Luca, Roberta Centorrino. Nasal High-Frequency Ventilation. Clinics in Perinatology, 2021, 48 (4), pp.761-782. 10.1016/j.clp.2021.07.006 . hal-04520381

HAL Id: hal-04520381

<https://hal.science/hal-04520381>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Nasal High Frequency Ventilation

Daniele De Luca (MD, PhD) (<https://orcid.org/0000-0002-3846-4834>)^{1*} - dm.deluca@icloud.com

and **Roberta Centorrino (MD)**² – roberta.centorrino@aphp.fr

^{1}Corresponding author – Professor of Neonatology and Chief of the Division of Pediatrics and Neonatal Critical Care, “A.Béclère” Medical Centre, Paris Saclay University Hospitals, APHP (Paris - France) & Physiopathology and Therapeutic Innovation Unit-INSERM U999, Paris Saclay University (Paris - France)*

² Assistant Professor (non-tenured) and Senior fellow Division of Pediatrics and Neonatal Critical Care, “A.Béclère” Medical Centre, Paris Saclay University Hospitals, APHP (Paris - France) & Physiopathology and Therapeutic Innovation Unit-INSERM U999, Paris Saclay University (Paris - France)

Contacts for both authors

Service de Pédiatrie et Réanimation Néonatale, Hôpital “A. Béclère”- GHU Paris Saclay, APHP

157 rue de la Porte de Trivaux, 92140 Clamart (Paris-IDF), France

Tel: +33 (0)145374837 - Fax: +33 (0)145374546

Conflicts of interest:

A/Prof. D. De Luca has received research grants, technical assistance and travel grants from Vyair inc. He also served as lecturer for Getinge inc. Dr. R. Centorrino received travel grant from from Vyair inc. These companies produce ventilators able to provide non-invasive high-frequency ventilations but had no role in the conception, writing or decide to submit this manuscript.

Key words: neonate, non-invasive, oscillation, percussive, rescue, respiratory support, interface, newborn infant

KEY POINTS

- The role of interface during non-invasive high-frequency ventilatory modes is very important and physical characteristics of different interfaces must be known in order to optimize their use.
- NHFOV needs to be used within a physiology-driven protocol with accurate mini-invasive multimodal monitoring and adequate nurse training. A protocol proposal is enclosed.
- NHFOV may be useful to reduce PaCO₂ and spare intubation and invasive ventilation in neonates with CPIP (i.e.: evolving BPD).
- Future trials about NHFOV need to be more explanatory and physiology-based.
- There is less experience about NHFPV, although it might be useful for TTN.

SYNOPSIS

Non-invasive high-frequency oscillatory (NHFOV) and percussive (NHFPV) ventilation represent two non-conventional techniques that may be useful in selected neonatal patients. We offer here a comprehensive review of physiology, mechanics and biology for both techniques. As NHFOV is the technique with the wider experience, we also provided a meta-analysis of available clinical trials, suggested ventilatory parameters boundaries and proposed a physiology-based clinical protocol to use NHFOV.

INTRODUCTION

The term “non-invasive high-frequency ventilation” designates a non-conventional ventilatory technique with supra-physiologic frequencies applied through an external non-invasive interface (nasal prongs, helmet or various types of mask), thus without endotracheal intubation or tracheostomy. It is out of our scopes to discuss whether conventional or non-conventional modalities are generally preferable but we will review the data regarding non-invasive high-frequency ventilations available in neonatology and their possible benefits.

Within this technique, we may recognize two modalities:

- non-invasive high-frequency oscillatory ventilation (NHFOV),
- non-invasive high-frequency percussive ventilation (NHFPV).

Only scanty exist about NHFPV, while NHFOV is quite often used in some countries.¹ The diffusion of NHFOV is likely due to the wide experience about the use of endotracheal high-frequency oscillatory ventilation (HFOV) and nasal continuous positive airway pressure (CPAP) in preterm neonates. The experience in HFOV and CPAP has pushed clinicians to combine them in order to maximize their advantages (such as, non-invasive interface, increase in functional residual capacity determining oxygenation improvement, no need for synchronization, efficient CO₂ removal).

PHYSIOLOGY OF NHFOV

General characteristics

NHFOV is based on the application of a continuous flow, generating a constant distending positive pressure with superimposed oscillations, delivered all over the spontaneous breathing cycle.

NHFOV could be applied either in a restrictive (e.g.: respiratory distress syndrome (RDS)) or in a mixed (e.g.: evolving broncho-pulmonary dysplasia (BPD) or BPD plus acute-on-chronic respiratory failure) respiratory insufficiency. NHFOV has the same basic principles and peculiar physiology in both cases: **Fig.1** shows similar flow, volume and pressures tracings recorded from active neonatal lung models of restrictive or mixed pattern ventilated with NHFOV.

Oscillations have constant frequency and may be seen as somehow similar to those of bubble CPAP, which provides a positive pressure with oscillations although the latter are smaller, irregular and with inconstant amplitude.² Furthermore, NHFOV can produce much higher mean airway pressure (P_{aw}) than bubble CPAP, since it is generated by a ventilator rather than a simple water valve.

A first interesting characteristic of NHFOV is that it can be easily used for alveolar recruitment increasing P_{aw} , without the risk of gas trapping-induced CO_2 retention, since this is avoided by the superimposed oscillations. Alveolar recruitment in NHFOV can be performed in a patient with restrictive respiratory failure in the same manner as it is done in endotracheal HFOV, following the well-known principles of the optimum lung volume strategy.³ Compared to endotracheal HFOV, however, NHFOV is generally accompanied by relevant pressure leaks that should be considered.⁴

If the effects on oxygenation are quite well known, the mechanisms of gas exchange during NHFOV are incompletely understood. They partially correspond to the ones occurring in endotracheal HFOV⁵ albeit with some peculiarities. During NHFOV a tidal volume is

spontaneously generated, but at the same time a small oscillatory volume is provided by the cyclic pressure oscillations and delivered all along the respiratory cycle.¹ These oscillations may be variably transmitted along the respiratory tree and this adds to the complexity of gas exchange, which is based on several physical phenomena.⁶

Oscillation transmission seems to be the most important variable influencing ventilation, although both tidal and oscillatory volumes actually contribute to gas exchange.^{7,8} This dual contribution has been initially hypothesized in *in vitro* measurements, but recent *in vivo* studies in preterm infants have provided consistent results.⁹ Bench data have also initially shown that NHFOV is able to wash-out CO₂ from the upper airways' deadspace.¹⁰ Subsequently, CO₂ clearance has been also demonstrated at lung level in similar bench models.¹¹ However, recent *in vivo* data demonstrated that during binasal prongs-delivered NHFOV, oscillations are not only transmitted to the upper airways but also to the alveolar tissue, especially in the non-gravity dependent and right-sided lung regions; this effect was noticed at relatively low oscillatory amplitude values.⁹ Nonetheless, these data may be significantly influenced by several factors. For instance, oscillation transmission is more efficient through stiff structures,¹² thus the amount of oscillatory volume reaching the alveoli may be different between babies with mainly restrictive and homogeneous (i.e.: RDS) and those with mixed and non-homogeneous patterns (i.e.: evolving BPD). Furthermore, type, size and material of interfaces may significantly influence the oscillation transmission and the resulting volume delivery (see below).¹ These can also be influenced by alveolar recruitment which changes the regional compliance.¹² On the other hand, patients' position could also have an effect, since neonates are often turned and this changes the non-gravity dependent lung zones. In adults, this shift has been associated with increased regional compliance and pulmonary perfusion and subsequent effects on volume delivery and oxygenation.^{13,14} An useful tool to summarize the interplay of factors influencing oscillation transmission is the oscillatory pressure ratio, that is, the

ratio between the oscillation amplitude set at the ventilator and that actually measured at a given level (e.g: at the interface or the pharynx).¹²

NHFOV and patient-ventilator interaction

Non-invasive ventilation is difficult to synchronize in neonates because of their high respiratory rate, low tidal volume and irregular breathing pattern. NHFOV bypasses this problem since all ventilations at supra-physiological frequencies, by definition, do not require synchronization. Furthermore, NHFOV could provide benefits over conventional non-invasive ventilations, because it does not induce phasic inspiratory glottal constriction, or decrease inspiratory glottal dilatation in newborn lambs.¹⁵ This may allow a more constant pressure/volume transmission to the distal airways.¹⁶ However, animal data also showed suppression of respiratory drive when nasal mask-delivered NHFOV was applied with a very low frequency (4 Hz).¹⁵ This effect has been confirmed in various models and is not mediated by hypocarbia, but rather by an increased vagal pulmonary stretch receptor or thoracic wall afferent activity.^{17,18} However, such low frequencies are not used in neonatology and an increased respiratory drive with consequent diaphragmatic activation has also been observed in animals: this depends on the ventilation parameters and is mediated by pulmonary rapidly adapting receptors.^{19,20} Conversely, in adults with central sleep apnea, nasal mask-delivered high-frequency oscillations stimulate respiratory effort in adult patients.²¹ In neonates, other mechanisms also influence the spontaneous respiratory drive, such as inflammation, pain or discomfort and the choice of NHFOV interface may play a relevant role (see below).²² Finally, as patients are spontaneously breathing during NHFOV, an increment in their work of breathing (WOB) could be observed, although this is lower in smaller patients.²³ WOB increment depends on many factors such as lung compliance and resistances, patients' size, ventilator type (see below) and parameters. Regarding these latter, lower frequencies seem to be associated with lower additional WOB:²⁴ this should be considered for long-lasting NHFOV, but also balanced with the need to deliver adequate ventilation. Therefore, the interactions between high-frequency oscillations

and spontaneous respiratory drive is complex and opposite effects might be observed in different patients or in different moments: tailoring ventilation with close patient monitoring is crucial.

Effect of different interfaces for NHFOV

NHFOV can be provided using different interfaces and each has its own mechanical characteristics and multiples effects on NHFOV physiology. Moreover, interfaces may significantly affect patients' comfort and the combination of these mechanisms can considerably change the effect of NHFOV in terms of oxygenation and gas exchange.

The first clinical experiences on NHFOV used single, long, high-resistive naso-pharyngeal tubes.²⁵ As demonstrated for CPAP, these interfaces were unsuitable and should not be used: in fact, they are associated with large leaks occurring through the contralateral nostril and with a relevant resistive load increasing the patients' WOB.²⁶ As short binasal prongs should be preferred over naso-pharyngeal tubes,²⁷ and nasal masks seems even better than short prongs,²⁸ we have investigated them in dedicated NHFOV bench studies finding efficient oscillation transmission and volume delivery.^{4,29,30} Finally, the use of prongs occluding only a small portion of the nostril cross-sectional area and connected via a long and resistive tubing (RAMCannula®) is currently spreading. These interfaces are particularly comfortable, however they provide high resistance, which increases the patients' WOB,³¹ and significant leaks when used to deliver CPAP^{32,33} or conventional non-invasive ventilation.³⁴ Despite these negative mechanical characteristics a case series described the use of RAMCannula®-delivered NHFOV in three neonates ventilated with relatively low Paw.³⁵

Our knowledge on the different interfaces for NHFOV and their effects on physiology can be resumed as follows:

1) The diameter of binasal prongs is important to guarantee an efficient ventilation (i.e.: the larger the probe, the greater the volume delivery); for a given amplitude and frequency, increasing the inspiratory time from 33% to 50%, allows a greater volume delivery, but increasing the amplitude beyond 50-60 cmH₂O does not significantly increase ventilation.^{29,30} Thus, when binasal prong-delivered NHFOV is provided with maximal parameters (that is, with amplitude of approximately 50-60 cmH₂O, a frequency of 8-10 Hz and 50% inspiratory time) a suitable oscillatory volume might be provided to neonates up to 1-1.5 Kg^{29,30} (if we consider 1-2 mL/Kg as an ideal target alike in invasive HFOV³⁶).

3) Nasal masks can efficaciously deliver NHFOV but provide lower oscillation transmission, due to the dampening occurring on the skin tissue and the mask soft material.⁴ This seems consistent with what happens during full face mask-delivered NHFOV in infants beyond neonatal age.⁷ More aggressive parameters (particularly lower frequency) may be needed to deliver the same oscillatory volume provided through binasal prongs.⁴ Nasal masks are associated with lower pressure leaks compared to nasal prongs³³ and these leaks (\approx 30-35%) seem similar during NHFOV and other types of non-invasive support.⁴ Bench data have demonstrated that moderate leakage may increase CO₂ clearance during NHFOV, probably facilitating the wash out from the upper airways deadspace and reducing gas trapping: thus, moderate leaks may be allowed, on a case-by-case evaluation.^{37,38}

3) RAMCannula® should not be used to deliver NHFOV, if it is applied in cases of severe respiratory failure (for instance, when intubation is pending) or for long periods or when the added resistance may have negative consequences (for instance, in extremely low birth weight neonates).

These mechanical data do not advocate for an universal use of a single interface. In fact, patients' comfort, ventilatory parameters, integrity of skin and also non-respiratory factors should be considered, as well. Moreover, the severity of respiratory failure may vary from one patient to the other and between different moments during the clinical course: thus, sometimes less aggressive parameters may be sufficient to compensate respiratory failure. Mechanical characteristics of

interfaces, patients' comfort and severity have a complex interplay on NHFOV physiology: therefore, the choice of NHFOV interface should be based on all these aspects and aim to find the best compromise between ventilation efficiency and patients' comfort.¹ This latter remains to be evaluated in specifically dedicated studies and, therefore, interfaces should be tailored on a case-by-case basis evaluation and interchanged to reduce the risk of skin lesions and according to patients' need.³⁹ **Tab.1** resumes the factors influencing gas exchange during NHFOV.

Different devices producing NHFOV

NHFOV may be applied with any ventilator able to provide the HFOV mode: several technologies are available.¹ From a formal point of view an actual "oscillatory" ventilation should have an active expiratory phase produced by a vibrating piston or membrane over a continuous gas flow or by an electronically controlled, cyclic flow reversal. These two ways to produce active oscillations have not been compared in respect to the application of NHFOV. Other technologies to produce HFOV (although without an active expiratory phase) are represented by the flow interruption due to the cyclic opening-closure of one or more pressure valves. Some neonatal ventilators are technically able to provide NHFOV using this technology, but their performance to provide invasive HFOV can be suboptimal at extreme settings or for late preterm/term neonates.^{40,41} As NHFOV is usually proposed for preterm infants, and, as bench studies have demonstrated an adequate ventilation for neonates up to 1-1.5 Kg,^{29,30} this is not likely to represent a significant problem. Another ventilator produces oscillations based on the inertia of gas in the circuit when the pressure at airway opening is rapidly changing: this technology is combined with fast responding inspiratory valves and high-flow capability but it has not been formally tested for NHFOV yet. There are also hybrid systems based on positive pressure generated by high flow nasal cannula with superimposed high-frequency oscillations provided by a solenoid valve: they have shown to provide efficacious CO₂ clearance in bench models.^{42,43} Finally, a new technology based on electronically controlled blower and valve

has been specifically proposed for NHFOV.⁴⁴ So far, hybrid high flow or blower and valve technologies have not been incorporated in any commercially available ventilator.

The active oscillation is considered important for the CO₂ clearance; however, the wide experience accumulated on invasive HFOV seems to indicate that this is not actually affecting clinical outcomes.⁴⁵ Nonetheless, at least in some patients, the kind of NHFOV-producing device may have an impact on its short-term efficiency.^{40,41} This problem may be less relevant in NHFOV, as this is supposed to be used in neonates below 1-1.5 kg. It is also important to note that, as patients are spontaneously breathing during NHFOV, a certain WOB may theoretically be superimposed by NHFOV application. This WOB increment is relatively low for preterm infants, but seems significantly different between ventilators based on the above-described technologies, with tendency to a lower WOB for ventilators with an active expiration.²⁴

Humidification during NHFOV

Heating and humidification during non-invasive respiratory support seem to improve comfort in adults, although we do not have specific neonatal data.⁴⁶ An European survey identified viscous secretions and consequent upper airway obstructions as specific side effects of NHFOV⁴⁷ and this seems logical as NHFOV is usually applied as rescue, when other non-invasive respiratory techniques have failed. The American Association for Respiratory Care suggest to use active humidification during non-invasive ventilation, although there are still open questions about the type of active humidifier to prefer.⁴⁶ Ullrich et al have studied humidification during NHFOV and found that aggressive NHFOV settings (i.e.: low frequency, high amplitude and IT) significantly reduced oropharyngeal gas conditioning.⁴⁸ This is consistent with data on CO₂ pharyngeal wash-out:¹⁰ thus, it seems reasonable to think that aggressive NHFOV remove water through physical mechanisms similar to those of HFOV gas exchange.⁵ The presence of leakage might also contribute, as gas particles can be mixed by thermo-diffusion and heat may be lost by thermal

conduction or with the entry of cool dry gas particles from the room air. The clinical relevance of these phenomena is unknown, but probably limited if NHFOV is not used for a longtime.

BIOLOGY OF NHFOV

Reddy and colleagues showed that superimposing oscillations over tidal volume excursions in a surfactant bubble lowers surface tension significantly more than tidal volume excursion alone.⁴⁹ Minimum surface tension decreased with increasing frequencies and reached a value of ≈ 7 mN/m at extreme frequencies (70-80 Hz), not attainable in clinical care. Conversely, minimum surface tension of 15-30 mN/m was measured with frequencies usually applied when using NHFOV. Similar values have been measured in neonates and infants with acute respiratory distress syndrome.^{50,51} Invasive HFOV improves lung mechanics and histology in surfactant-depleted rabbits.⁵² Consistent findings, as well as larger surfactant aggregates have been reported in animal models mimicking different types of lung injury.^{53,54} These data allow to hypothesize that NHFOV could improve surfactant function, although this only remains a working hypothesis.

EVIDENCE-BASED REVIEW OF CLINICAL DATA ON NHFOV

Uncontrolled studies

In 2016 we have analyzed the clinical data on NHFOV available at that time and these were mainly represented by uncontrolled small case series, showing globally promising results.¹ Because of the neonatal experience on HFOV and wide availability of this ventilatory mode, NHFOV spread in the last five years led to the publication of other similar studies. These latest uncontrolled studies were consisting with the earlier data, reporting that: 1) NHFOV may reduce the extubation failure or the need of invasive ventilation in infants with pending intubation; 2) NHFOV may improve gas exchange; 3) NHFOV may reduce the number of apneic spells; 4) NHFOV did not cause any severe adverse event.⁵⁵⁻⁵⁸ The absence of these had also been suggested by an European survey of physicians using NHFOV.⁴⁷

Randomized controlled trials

After these studies, randomized controlled trials finally started to be published. We performed a systematic review of these trials. A literature search was performed on PubMed (on November 7, 2020), using “nasal” or “non-invasive high-frequency oscillatory ventilation” or “NHFOV”, as words or MeSH terms, without year or language restrictions. We also hand-searched references cited in the studies identified through the initial search, review articles and the authors’ personal archives. We excluded “grey” literature, unpublished or non-peer reviewed reports. Non-English manuscripts were translated using Google translator. We used a data extraction sheet based on the Cochrane Review Group template adapted from our previous work.⁵⁹ Data from included trials were extracted and cross-verified independently by the two authors. We analyzed data applying the Sidik-Jonkman method⁶⁰ with random-effects models. Consistency was evaluated using the I^2 statistics and χ^2 test for heterogeneity. Meta-regressions were performed adjusting for gestational age and prenatal steroids as confounders. We inserted one covariate in each model in order to reduce false positive results.⁵⁹ Analyses were performed with Open-MetaAnalyst 10.1.⁶¹

Meta-analysis of randomized controlled trials

To date, there are 11 trials comparing NHFOV against single level or biphasic CPAP, either with parallel or crossover design, mainly having short-term events or gas exchange as primary outcomes.^{62–72} **Tab.2** shows essential trials’ characteristics. All but two trials^{63,68} recruited relatively small populations and three enrolled extremely preterm neonates.^{62,65,70} The majority of primary outcomes were represented by short-term need for intubation and invasive ventilation (IMV)^{63,66,68,71} or PaCO₂/oxygenation.^{62,63,65,67,72} While authors should be commended for the efforts, there are important problems behind these outcomes’ choice:

1. The need for IMV can be a sensible outcome, however some studies investigated NHFOV in preterm neonates with RDS as primary respiratory support (i.e.: before surfactant

administration, if any)^{64,68} and others as secondary support after extubation or surfactant administration.^{63,66,67,69,71,72} This lack of homogeneity prevents to draw any conclusion: although it seems logical that a higher Paw would reduce the risk of extubation failure as demonstrated for other non-invasive respiratory support techniques,^{73,74} we need larger trials focused on the post-extubation phase, comparing NHFOV with other non-invasive techniques. More and above this, we need to actually use higher Paw during NHFOV: in the majority of trials, Paw was equivalent in the two arms,^{62,64,65,68-72} and this would prevent NHFOV to provide an actual recruitment. Furthermore, it is unclear what might be the advantage of NHFOV in the early phase of RDS. In fact, it is known that CPAP works very well for the majority of patients in this phase⁷⁵ and, when CPAP fails, that is usually for worsening oxygenation. Oxygenation impairment in a purely restrictive and homogeneous condition (such as RDS) is easily overcome by alveolar recruitment. However, since trials investigating NHFOV as a primary mode always used an equivalent Paw in the two arms,^{64,68} no alveolar recruitment was provided and it was logical to observe no difference. Moreover, if alveolar recruitment through NHFOV would be applied in this phase, this might delay surfactant replacement, reducing its efficacy, which is optimal only within the first 3h of life.^{76,77}

2. HFOV is known to be very powerful in washing-out CO₂. Because NHFOV has some peculiar physiologic characteristics, it was interesting to evaluate its carbon dioxide clearance capacity, although it would have been unlikely to see NHFOV failing on this regard. In fact, face mask-delivered NHFOV has been found to effectively washout CO₂ also in a small crossover trial enrolling adults.⁷⁸ However, CO₂ clearance has been tested in trials enrolling stable preterm neonates or anyway with relatively low PaCO₂ levels and no respiratory acidosis.^{62,63,65-67,69,72} This choice has led to less meaningful and possibly biased results, since, in the daily NICU care, no one would shift a patient from CPAP to NHFOV if there is no hypercarbia. Moreover, having CO₂ clearance as outcome also presents a

problem similar to the afore-mentioned issue about Paw and oxygenation. In fact, some trials used a flow interruption device, generating very low amplitudes which are unlikely to be transmitted downstream:^{62,68,71,72} the generation of a very little oscillatory volume and its actual contribution to gas exchange is doubtful.

Two large well designed physiology-driven multicenter trials, are currently ongoing.¹ These trials aim to verify if NHFOV provides any benefit, compared to CPAP or non-invasive positive pressure ventilation, either as primary respiratory support or in the post-extubation phase for preterm neonates with RDS.^{79,80}

The trials published so far had a panoply of secondary outcomes, amongst which, there are some difficult to improve, but also several vital parameters and safety data. NHFOV reduced the number of desaturations and bradycardia in one trial,⁷⁰ while there was no difference in any safety data in the other trials.^{62-69,71,72} Therefore, we can reasonably state that NHFOV is essentially safe or can even be beneficial in reducing bradycardia, desaturations and/or apneas, at least in some patients. However, due to the complex effects of NHFOV on the spontaneous breathing (see above), these results cannot be generalized as they can change according to the patient's clinical condition, cointerventions, NHFOV interfaces and parameters.

We present here the meta-analysis of trials focusing on the two more commonly studied outcomes: 1) need for intubation and mechanical ventilation; 2) PaCO₂ levels after NHFOV application (**Fig.2**). NHFOV significantly reduces the risk of intubation and need of IMV (odds ratio: 0.29; 95% confidence interval: 0.2-0.4; $p < 0.001$) compared to single level or biphasic CPAP. These results are confirmed if we only analyze the trial using NHFOV as post-extubation support (odds ratio: 0.3; 95% confidence interval: 0.18-0.5; $p < 0.001$). NHFOV also tends to reduce CO₂ compared to single level or biphasic CPAP (mean difference: -4.6 mmHg; 95% confidence interval: -9.3-0.08; $p = 0.05$); significant heterogeneity is seen for this outcome and this may be related to the

different times and techniques to measure PaCO₂ and to the different ventilatory strategies described above.

We further studied the effect of possible confounders: for the outcome intubation, neither gestational age (coefficient: 0.104; (95% confidence interval: -0.2; 0.4), $p=0.527$), nor prenatal steroids (coefficient: -0.007; (95% confidence interval: -0.02; 0.007), $p=0.327$), were associated with the effect size; same results were found for PaCO₂ levels, regarding gestational age (coefficient: -1.1 (95% confidence interval: -2.7; 0.4), $p=0.137$) and prenatal steroids (coefficient: 0.07 (95% confidence interval: -0.1; 0.2), $p=0.424$).

These results, and particularly those issued by subgroup analyses and meta-regressions, should be cautiously seen also in light of the above-described problems in trial design and outcome choice. The NHFOV trials published so far have been affected by significant intrinsic biases and these have been reported in commenting letters.^{81,82} We do not comment here all the biases, as this would be beyond our scopes. Nonetheless, future trials shall investigate NHFOV with a physiology-driven management, in homogeneous populations, with a clearly defined lung mechanics and restricted, physiopathologically sound objectives. NHFOV shall be compared to a well-defined “control” technique and both shall be applied with a strict protocol. In other words, future trials should have an explanatory design and tend to recruit only from well experienced sites. More pragmatic inclusive approaches are unsuitable because they seek a ‘real world’ answer for a more widely used and well-known intervention.⁸³ On the contrary, NHFOV is a relatively new technique and, by mixing different populations or leaving ventilatory management too free, we risk to lose important information.⁸⁴

To date, according to the available clinical data and the physiology background, NHFOV can be considered as an additional technique for infants with severe respiratory failure. It may be suitable

in preterm patients with pending re-intubation or in those with evolving BPD, where one may want to spare oxygen exposure and invasive ventilation as much as possible. In these cases, NHFOV can be used, if there is enough expertise, after careful evaluation on a case-by-case scenario and with accurate patients' monitoring and physiology-based management.

PERSONAL EXPERIENCE AND PROTOCOL TO MANAGE NHFOV

As NHFOV represents another “brick in the wall” of the non-invasive respiratory support,⁸⁵ we have been using it for extremely preterm infants with evolving BPD to reduce invasive ventilation as much as possible. These patients are comprised under the definition of chronic pulmonary insufficiency of prematurity (CPIP), recently issued by the International Neonatal Consortium, which spans as a *continuum* from the end of the first week of life to 36 weeks' post-conceptual age.⁸⁶ During this period, in our experience, some extremely preterm infants show a worsening of their respiratory function around 14 days of postnatal age and this can be easily visualized with semi-quantitative lung ultrasound.⁸⁷

Our NHFOV protocol follows a physiology based-approach, with alveolar recruitment maneuvers alike in endotracheal HFOV³ and close multimodal monitoring, based on semiquantitative lung ultrasound,⁸⁸ transcutaneous blood gas measurements, peripheral saturation and perfusion index.⁸⁹ Lung ultrasound is used to assess lung aeration and guide the alveolar recruitment in real-time as described in critically ill adults.⁹⁰ Nurses are specifically trained to care for these infants who are considered at high risk: non-pharmacological sedation is widely given, hydrocolloid gels are used and interfaces are swapped to change the pressure points and reduce the risk of skin injuries. COMFORT⁹¹ and/or EDIN⁹² scores are serially used to evaluate patients comfort. Our proposal also integrates different respiratory techniques and respiratory support is personalized.

As shown in **Fig.3**, the respiratory management is initially based on gas exchange traits. Due to its capability to wash-out CO₂, NHFOV is used as first intention in extremely preterm infants experiencing hypercapnic respiratory failure. Conventional non-invasive respiratory support is initially used in infants with hypoxemic respiratory failure and NHFOV is regarded as rescue intervention in case of failure; conventional non-invasive ventilation is synchronized, either using neurally adjusted ventilator assist⁹³ or flow/pressure-sensors in order to increase its efficacy and optimize patient-ventilator interaction (more details in the figure legend). Point-of care echocardiography is also performed according to international guidelines:⁹⁴ when there are signs of pulmonary hypertension and this significantly influences hypoxia, nebulized iloprost is started,⁹⁵ using modern vibrating-mesh nebulizers on the inspiratory limb.⁹⁶ Thus, intubation and inhaled nitric oxide are only considered as last resource. When the monitoring shows consistent signs of improvement, the respiratory support is de-escalated and can go back to CPAP, which is usually weaned between 33 and 34' weeks post-conceptual age. An illustrative case of a patient managed with this respiratory strategy has been described in our previous review on NHFOV.¹

This is obviously just a proposal for a respiratory management protocol integrating NHFOV for neonates with evolving BPD. **Tab.3** shows suggested boundaries for NHFOV in our strategy. Other possible strategies exist and, for example, NHFOV has been proposed also as first line technique in neonates with RDS.¹ However, the use of NHFOV later in life for neonates with CPIP seems to us more reasonable and well grounded. It is actually difficult to design randomized controlled trials for these patients, but in absence of these studies, the respiratory care should be tailored to the patients' characteristics as much as possible.

EXPERIENCES WITH NHFPV

High-frequency percussive ventilation is a pneumatic, pressure-limited, time-cycled, high-frequency ventilation providing sub-physiological volumes generated by Venturi's effect through a

sliding device (called Phasitron®) powered by high-flow compressed gas inlet. Thus, the high frequency volume delivery is provided as gas “percussions” into the airways. Between 90 to 650 percussions per minute can be provided. These percussions are superimposed to a pressure-limited, conventional respiratory support with physiological rate and volume: conventional frequency, IT and positive end-expiratory pressure need to be set as usual. An end-expiratory pressure for the gas percussions must be set, while the peak pressure is decided through the value of pulsatile gas flow (the greater the flow, the higher is the peak pressure reached all along the conventional respiratory cycle). A typical pressure waveform during this modality is shown in **Fig.4**: conventional breaths are drawn with superimposed percussions. Since the percussions are generated through the Venturi effect, the ventilator circuit has an open expiratory limb and the patient may spontaneously breath without any added WOB. Only one ventilator can provide this modality, which can be delivered both endotracheally or as NHFPV. This modality has the physical capability to improve secretions clearance and to move secretions towards upper airways. Because of these characteristics, this modality has been mainly used for aspiration-induced lung injuries and acute respiratory distress syndrome, both in adults and children.⁹⁷

In neonatology, NHFPV has been investigated in a randomized controlled trial to treat transient tachypnoea of the neonate (TTN): NHFPV was superior to CPAP in improving oxygenation and reducing the duration of TTN.⁹⁸ In a second work, the same authors showed that NHFPV is safe in terms of cerebral oxygenation in neonates with TTN or moderate RDS.⁹⁹ Since TTN is due to a lack of lung fluid reabsorption, these results seem physiopathologically plausible as NHFPV may have facilitated the lung fluid clearance. Given its physical characteristics, NHFPV might also be theoretically useful in meconium aspiration, alike for other inhalation syndromes in older patients. Interestingly, endotracheal high frequency percussive ventilation compared to HFOV resulted in a better oxygenation in animal model of meconium aspiration,¹⁰⁰ while the two techniques resulted equivalent in a model of lung injury caused by depleting lung lavages.¹⁰¹ Furthermore, two other

animal studies compared the long-term effect of NHFPV and invasive ventilation in preterm lambs mimicking infants with chronic pulmonary insufficiency of prematurity (i.e.: evolving BPD). The animals ventilated with NHFPV for three weeks showed improved alveolarization with increased surfactant protein-B expression and better oxygenation.^{102,103} These findings may be at least partially explained by an enhanced PTHrP-PPAR γ -mediated epithelial/mesenchymal signaling of alveolarization.¹⁰² These results allow to hypothesize that long-term respiratory support with NHFPV, or a strategy integrating different non-invasive non-conventional respiratory supports, might be useful to improve long-term respiratory outcomes in preterm infants. In conclusion, the use of NHFPV for TTN seems interesting, but given its complexity, the mildness of TTN and the effectiveness of CPAP, it is unclear if NHFPV may be really useful.

ACKNOWLEDGEMENTS

Authors are grateful to Alejandro Alonso for the artwork and to Prof. Giorgio Conti, for the modeling of NHFOV.

Best Practices

REFERENCES

1. De Luca D, Dell'Orto V. Non-invasive high-frequency oscillatory ventilation in neonates: review of physiology, biology and clinical data. *Arch Dis Child Fetal Neonatal Ed* 2016;101:F565-F570.
2. Pillow JJ, Hillman N, Moss TJM, et al. Bubble Continuous Positive Airway Pressure Enhances Lung Volume and Gas Exchange in Preterm Lambs. *Am J Resp Crit Care Med* 2007;176:63-69.

- 3.**De Jaegere A, van Veenendaal MB, Michiels A, et al.Lung Recruitment Using Oxygenation during Open Lung High-Frequency Ventilation in Preterm Infants.
Am J Resp Crit Care Med 2006;174:639-645.
- 4.**Centorrino R, Dell’Orto V, Gitto E, et al.Mechanics of nasal mask-delivered HFOV in neonates: A physiologic study.Pediatr Pulmonol 2019;54:1304-1310.
- 5.**Pillow JJ.High-frequency oscillatory ventilation: mechanisms of gas exchange and lung mechanics.Crit Care Med 2005;33(3 Suppl):S135-141.
- 6.**Boynton BR, Hammond MD, Fredberg JJ, et al.Gas exchange in healthy rabbits during high-frequency oscillatory ventilation.J Appl Physiol 1989;66:1343-1351.
- 7.**De Luca D, Costa R, Visconti F, et al.Oscillation transmission and volume delivery during face mask-delivered HFOV in infants: Bench and in vivo study: Noninvasive HFOV Feasibility in Infants.Pediatr Pulmonol 2016;51:705-712.
- 8.**De Luca D, Costa R, Spinazzola G, et al.Oscillation Transmission and Ventilation during Face Mask-Delivered High Frequency Oscillatory Ventilation in Infants: a Bench Study with Active Lung Simulator.Arch Dis Child 2012;97(Suppl 2):A117-A118.
- 9.**Gaertner VD, Waldmann AD, Davis PG, et al.Transmission of Oscillatory Volumes into the Preterm Lung during Noninvasive High-Frequency Ventilation.
Am J Respir Crit Care Med 2020 Oct 23.doi:10.1164/rccm.202007-2701OC
- 10.**Mukerji A, Finelli M, Belik J.Nasal high-frequency oscillation for lung carbon dioxide clearance in the newborn.Neonatology 2013;103:161-165.
- 11.**Sivieri EM, Eichenwald EC, Rub DM, et al.An in-line high frequency flow interrupter applied to nasal CPAP: Improved carbon dioxide clearance in a premature infant lung model.
Pediatr Pulmonol 2019;54:1974-1981.
- 12.**van Genderingen HR, Versprille A, Leenhoven T, et al.Reduction of oscillatory pressure along the endotracheal tube is indicative for maximal respiratory compliance during high-frequency oscillatory ventilation: A mathematical model study.Pediatr Pulmonol 2001;31:458-463.

- 13.**Prisk GK, Yamada K, Henderson AC, et al. Pulmonary perfusion in the prone and supine postures in the normal human lung. *J Appl Physiol* 2007;103:883-894.
- 14.**Nyrén S, Radell P, Lindahl SGE, et al. Lung Ventilation and Perfusion in Prone and Supine Postures with Reference to Anesthetized and Mechanically Ventilated Healthy Volunteers. *Anesthesiology* 2010;112:682-687.
- 15.**Hadj-Ahmed MA, Samson N, Nadeau C, et al. Laryngeal Muscle Activity during Nasal High-Frequency Oscillatory Ventilation in Nonsedated Newborn Lambs. *Neonatology* 2015;107:199-205.
- 16.**Owen LS, Morley CJ, Dawson JA, et al. Effects of non-synchronised nasal intermittent positive pressure ventilation on spontaneous breathing in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2011;96:F422-428.
- 17.**Kohl J, Freund U, Koller EA. Reflex apnea induced by high-frequency oscillatory ventilation in rabbits. *Respir Physiol* 1991;84:209-222.
- 18.**England SJ, Onayemi A, Bryan AC. Neuromuscular blockade enhances phrenic nerve activity during high-frequency ventilation. *J Appl Physiol* 1984;56:31-34.
- 19.**Kohl J, Scholz U, Glowicki K, et al. Discharge of pulmonary rapidly adapting stretch receptors during HFO ventilation. *Respir Physiol* 1992;90:115-124.
- 20.**Kohl J, Koller EA. Blockade of pulmonary stretch receptors reinforces diaphragmatic activity during high-frequency oscillatory ventilation. *Pflugers Arch* 1988;411:42-6.
- 21.**Henke KG, Sullivan CE. Effects of high-frequency pressure waves applied to upper airway on respiration in central apnea. *J Appl Physiol* 1992;73:1141-1145.
- 22.**Di Fiore JM, Martin RJ, Gauda EB. Apnea of prematurity-Perfect storm. *Respir Physiol Neurobiol* 2013;189:213-22.
- 23.**van Heerde M, van Genderingen H, Leenhoven T, et al. Imposed work of breathing during high-frequency oscillatory ventilation: a bench study. *Crit Care* 2006;10:R23. doi:10.1186/cc3988

- 24.**Bordessoule A, Piquilloud L, Lyazidi A, et al.Imposed Work of Breathing During High-Frequency Oscillatory Ventilation in Spontaneously Breathing Neonatal and Pediatric Models. *Respir Care* 2018;63:1085-1093.
- 25.**van der Hoeven M, Brouwer E, Blanco CE.Nasal high frequency ventilation in neonates with moderate respiratory insufficiency.*Arch Dis Child Fetal Neonatal Ed* 1998;79:F61-63.
- 26.**De Paoli AG, Lau R, Davis PG et al.Pharyngeal pressure in preterm infants receiving nasal continuous positive airway pressure.*Arch Dis Child Fetal Neonatal Ed* 2005;90:F79-F81.
- 27.**De Paoli AG, Davis PG, Faber B, et al.Devices and pressure sources for administration of nasal continuous positive airway pressure (NCPAP) in preterm neonates. *Cochrane Database Syst Rev* 2002;(4):CD002977.
- 28.**Jasani B, Ismail A, Rao S, Patole S. Effectiveness and safety of nasal mask versus binasal prongs for providing continuous positive airway pressure in preterm infants-A systematic review and meta-analysis. *Pediatr Pulmonol* 2018;53:987-992.
- 29.**De Luca D, Carnielli VP, Conti G, Piastra M.Noninvasive high frequency oscillatory ventilation through nasal prongs: bench evaluation of efficacy and mechanics. *Intensive Care Med* 2010;36:2094-2100.
- 30.**De Luca D, Piastra M, Pietrini D, Conti G.Effect of amplitude and inspiratory time in a bench model of non-invasive HFOV through nasal prongs.*Pediatr Pulmonol* 2012;47:1012-1018.
- 31.**Green EA, Dawson JA, Davis PG, et al.Assessment of resistance of nasal continuous positive airway pressure interfaces. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F535-F539.
- 32.**Gerdes JS, Sivieri EM, Abbasi S. Factors influencing delivered mean airway pressure during nasal CPAP with the RAM cannula: Factors Affecting MAP During NCPAP With RAM Cannula. *Pediatr Pulmonol* 2016;51:60-69.
- 33.**Sharma D, Murki S, Maram S, et al.Comparison of delivered distending pressures in the oropharynx in preterm infant on bubble CPAP and on three different nasal interfaces. *Pediatr Pulmonol* 2020;55:1631-1639.

- 34.**Mukerji A, Belik J.Neonatal nasal intermittent positive pressure ventilation efficacy and lung pressure transmission.J Perinatol 2015;35:716-719.
- 35.**Aktas S, Unal S, Aksu M, et al.Nasal HFOV with Binasal Cannula Appears Effective and Feasible in ELBW Newborns. J Trop Pediatr 2016;62:165-168.
- 36.**Ventre KM, Arnold JH. High frequency oscillatory ventilation in acute respiratory failure. Paediatr Respir Rev 2004;5:323-332.
- 37.**Klotz D, Schaefer C, Stavropoulou D, et al.Leakage in nasal high-frequency oscillatory ventilation improves carbon dioxide clearance-A bench study.Pediatr Pulmonol 2017;52:367-372.
- 38.**Schäfer C, Schumann S, Fuchs H, et al.Carbon dioxide diffusion coefficient in noninvasive high-frequency oscillatory ventilation.Pediatr Pulmonol 2019;54:759-764.
- 39.**De Luca D, Servel AC, de Klerk A.Noninvasive Ventilation Interfaces and Equipment in Neonatology. In: Noninvasive Mechanical Ventilation and Difficult Weaning in Critical Care. New York: Springer-Verlag International; 2015. doi:10.1007/978-3-319-04259-6
- 40.**Tingay DG, John J, Harcourt ER, et al.Are All Oscillators Created Equal? In vitro Performance Characteristics of Eight High-Frequency Oscillatory Ventilators. Neonatology. 2015;108:220-228.
- 41.**Grazioli S, Karam O, Rimensberger PC.New Generation Neonatal High Frequency Ventilators: Effect of Oscillatory Frequency and Working Principles on Performance. Respir Care 2015;60:363-370.
- 42.**Sivieri EM, Eichenwald E, Bakri SM, et al.Effect of high frequency oscillatory high flow nasal cannula on carbon dioxide clearance in a premature infant lung model: A bench study. Pediatr Pulmonol 2019;54: 436-443.
- 43.**Rub DM, Sivieri EM, Abbasi S, et al.Effect of high-frequency oscillation on pressure delivered by high flow nasal cannula in a premature infant lung model. Pediatr Pulmonol 2019;54:1860-1865.

- 44.** Yuan Y, Sun J, Wang B, et al. A noninvasive high frequency oscillation ventilator: Achieved by utilizing a blower and a valve. *Rev Sci Instrum* 2016;87:025113.
- 45.** Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2015;(3):CD000104.
- 46.** Restrepo RD, Walsh BK. Humidification During Invasive and Noninvasive Mechanical Ventilation: 2012. *Respir Care* 2012;57:782-788.
- 47.** Fischer HS, Bohlin K, Bühler C, et al. Nasal high-frequency oscillation ventilation in neonates: a survey in five European countries. *Eur J Pediatr* 2015;174:465-471.
- 48.** Ullrich TL, Czernik C, Bühler C, et al. Nasal high-frequency oscillatory ventilation impairs heated humidification: A neonatal bench study. *Pediatr Pulmonol* 2017;52:1455-1460.
- 49.** Reddy PI, Al-Jumaily AM, Bold GT. Dynamic surface tension of natural surfactant extract under superimposed oscillations. *J Biomech* 2011;44:156-163.
- 50.** Autilio C, Echaide M, De Luca D, et al. Controlled hypothermia may improve surfactant function in asphyxiated neonates with or without meconium aspiration syndrome. *PLoS One* 2018;13:e0192295.
- 51.** De Luca D, Lopez-Rodriguez E, Minucci A, et al. Clinical and biological role of secretory phospholipase A2 in acute respiratory distress syndrome infants. *Crit Care*. 2013;17:R163.
- 52.** Simma B, Luz G, Trawöger R, et al. Comparison of different modes of high-frequency ventilation in surfactant-deficient rabbits. *Pediatr Pulmonol* 1996;22:263-270.
- 53.** Kerr CL, Veldhuizen RAW, Lewis JF. Effects of High-Frequency Oscillation on Endogenous Surfactant in an Acute Lung Injury Model. *Am J Resp Crit Care Med* 2001;164:237-242.
- 54.** Aspros AJ, Coto CG, Lewis JF, et al. High-frequency oscillation and surfactant treatment in an acid aspiration model. *Can J Physiol Pharmacol* 2010;88:14-20.
- 55.** Ali YAH, Seshia MM, Ali E, et al. Noninvasive High-Frequency Oscillatory Ventilation: A Retrospective Chart Review. *Am J Perinatol* 2020 Oct 19. doi:10.1055/s-0040-1718738.

- 56.** Thatrimontrichai A, Sirianansopa K, Janjindamai W, et al. Comparison of Endotracheal Reintubation between Nasal High-Frequency Oscillation and Continuous Positive Airway Pressure in Neonates. *Am J Perinatol* 2020;37:409-414.
- 57.** Łoniewska B, Tousty J, Michalczyk B, et al. The Use of Noninvasive Ventilation with High Frequency in Newborns—A Single-Center Experience. *Am J Perinatol* 2019;36:1362-1367.
- 58.** Binmanee A, el Helou S, Shivananda S, et al. Use of high noninvasive respiratory support pressures in preterm neonates: a single-center experience. *J Matern Fetal Neonatal Med* 2017;30:2838-2843.
- 59.** Tridente A, De Martino L, De Luca D. Porcine vs bovine surfactant therapy for preterm neonates with RDS: systematic review with biological plausibility and pragmatic meta-analysis of respiratory outcomes. *Respir Res* 2019;20:28. doi:10.1186/s12931-019-0979-0.
- 60.** Inthout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol* 2014;14:25. doi:10.1186/1471-2288-14-25.
- 61.** Wallace BC, Schmid CH, Lau J, et al. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. *BMC Med Res Methodol* 2009;9:80. doi:10.1186/1471-2288-9-80.
- 62.** Bottino R, Pontiggia F, Ricci C, et al. Nasal high-frequency oscillatory ventilation and CO₂ removal: A randomized controlled crossover trial. *Pediatr Pulmonol* 2018;53:1245-1251.
- 63.** Chen L, Wang L, Ma J, et al. Nasal High-Frequency Oscillatory Ventilation in Preterm Infants With Respiratory Distress Syndrome and ARDS After Extubation. *Chest* 2019;155:740-748.
- 64.** Iranpour R, Armanian AM, Abedi AR, et al. Nasal high-frequency oscillatory ventilation (nHFOV) versus nasal continuous positive airway pressure (NCPAP) as an initial therapy for respiratory distress syndrome (RDS) in preterm and near-term infants. *BMJ Paediatr Open* 2019;3:e000443.
- 65.** Klotz D, Schneider H, Schumann S, et al. Non-invasive high-frequency oscillatory ventilation in preterm infants: a randomised controlled cross-over trial.

Arch Dis Child Fetal Neonatal Ed 2018;103:F1-F5.

66.Lou W, Zhang W. Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in premature infants with respiratory distress syndrome after weaning: A randomized controlled trial. *Guangdong Med J* 2017;38:2037-2040.

67.Lou W, Zhang W, Yuan L, et al. Comparative study of noninvasive high-frequency oscillatory ventilation and bilevel positive airway pressure ventilation for preterm infants with respiratory distress syndrome. *Chinese Gen Pract* 2018;21:1983-1988.

68.Malakian A, Bashirnezhadkhabaz S, Aramesh MR, et al. Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: a randomized controlled trial. *J Mater Fetal Neonatal Med* 2020;33:2601-2607.

69.Mukerji A, Sarmiento K, Lee B, et al. Non-invasive high-frequency ventilation versus bi-phasic continuous positive airway pressure (BP-CPAP) following CPAP failure in infants <1250g: a pilot randomized controlled trial. *J Perinatol* 2017;37:49-53.

70.Rüegger CM, Lorenz L, Kamlin COF, et al. The Effect of Noninvasive High-Frequency Oscillatory Ventilation on Desaturations and Bradycardia in Very Preterm Infants: A Randomized Crossover Trial. *J Pediatr* 2018;201:269-273.e2.

71.Zhu XW, Zhao JN, Tang SF, et al. Noninvasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with moderate-severe respiratory distress syndrome: A preliminary report. *Pediatr Pulmonol* 2017;52:1038-1042.

72.Zhu X, Yan J, Ran Q, et al. Noninvasive high-frequency oscillatory ventilation versus for respiratory distress syndrome in preterm infants: a preliminary report. *Chin J Neonatol* 2017;32:291-294.

73.Buzzella B, Claire N, D'Ugard C, et al. A Randomized Controlled Trial of Two Nasal Continuous Positive Airway Pressure Levels after Extubation in Preterm Infants. *J Pediatr* 2014;164:46-51.

- 74.**Lemyre B, Davis PG, De Paoli AG, et al.Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation.Cochrane Database Syst Rev 2017;2:CD003212.
- 75.**Subramaniam P, Ho JJ, Davis PG.Prophylactic nasal continuous positive airway pressure for preventing morbidity and mortality in very preterm infants.
Cochrane Database Syst Rev 2016;6:CD001243.
- 76.**Raschetti R, Yousef N, Vigo G, et al.Echography-Guided Surfactant Therapy to Improve Timeliness of Surfactant Replacement:A Quality Improvement Project. J Pediatr 2019;212:137-143.
- 77.**Bahadue FL, Soll R.Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome.Cochrane Database Syst Rev 2012;11:CD001456.
- 78.**Esquinas A, Mantellini E, Benitez Leon F, et al.International study use of high frequency chest wall oscillation (HFCWO) in secretion management in the mechanically ventilated patient. Proceedings of ESICM 2010 Congress.Intensive Care Med 2010;36(S2):105(n.0080).
doi:10.1007/s00134-010-1999-x
- 79.**Zhu XW, Shi Y, Shi LP et al.NHFOV Study Group.Non-invasive high-frequency oscillatory ventilation versus nasal continuous positive airway pressure in preterm infants with respiratory distress syndrome: Study protocol for a multi-center prospective randomized controlled trial. Trials 2018;19: 319.
- 80.**Shi Y, De Luca D.NASal OscillatioN post-Extubation (NASONE) study group.Continuous positive airway pressure (CPAP) vs noninvasive positive pressure ventilation (NIPPV) vs noninvasive high frequency oscillation ventilation (NHFOV) as post-extubation support in preterm neonates: protocol for an assessor-blinded, multicenter, randomized controlled trial.
BMC Pediatr 2019;19:256.
- 81.**De Luca D.Noninvasive high-frequency ventilation and the errors from the past: designing simple trials neglecting complex respiratory physiology.J Perinatol 2017;37:1065-1066.

- 82.**Fischer HS, Rimensberger PC.Early noninvasive high-frequency oscillatory ventilation in the primary treatment of respiratory distress syndrome.Pediatr Pulmonol 2018;53:126-127.
- 83.**Thorpe KE, Zwarenstein M, Oxman AD, et al.A pragmatic–explanatory continuum indicator summary (PRECIS): a tool to help trial designers.J Clin Epidemiol 2009;62:464-475.
- 84.**De Luca D, Harrison D, Peters MJ.‘Lumping or Splitting’ in Paediatric Acute Respiratory Distress Syndrome (PARDS).Intensive Care Med 2018;44:1548-1550.
- 85.**Gregoretti C, Cortegiani A, Maggiore SM.Noninvasive oscillatory ventilation (NHFOV) in infants: Another brick in the wall of paediatric noninvasive ventilation? Pediatr Pulmonol 2016;51:663-664.
- 86.**Steinhorn R, Davis JM, Göpel W, et al.Chronic Pulmonary Insufficiency of Prematurity: Developing Optimal Endpoints for Drug Development.J Pediatr 2017;191:15-21.e1.
- 87.**Loi B, Vigo G, Baraldi E, et al. LUSTRE study group.Lung Ultrasound to Monitor Extremely Preterm Infants and Predict BPD: Multicenter Longitudinal Cohort Study. Am J Respir Crit Care Med 2020 Dec 22.doi:10.1164/rccm.202008-3131OC
- 88.**Brat R, Yousef N, Klifa R, et al.Lung Ultrasonography Score to Evaluate Oxygenation and Surfactant Need in Neonates Treated With Continuous Positive Airway Pressure. JAMA Pediatr 2015;169:e151797.
- 89.**De Luca D, Romain O, Yousef N, et al.Monitorages physiopathologiques en réanimation néonatale.J Pédiatrie Puericulture 2015;28:276-300.doi:10.1016/j.jpp.2015.06.004
- 90.**Tusman G, Acosta CM, Costantini M.Ultrasonography for the assessment of lung recruitment maneuvers Crit Ultrasound J 2016;8:8.
- 91.**van Dijk M, Peters JWB, van Deventer P, et al.The COMFORT Behavior Scale: a tool for assessing pain and sedation in infants.Am J Nurs 2005;105:33-36.
- 92.**Debillon T, Zupan V, Ravault N, et al.Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. Arch Dis Child Fetal Neonatal Ed 2001;85:F36-41.

- 93.**Piastra M, De Luca D, Costa R, et al.Neurally adjusted ventilatory assist vs pressure support ventilation in infants recovering from severe acute respiratory distress syndrome: nested study. *J Crit Care* 2014;29:312.e1-312.e5.
- 94.**Singh Y, Tissot C, Fraga MV, et al.International evidence-based guidelines on Point of Care Ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). *Crit Care* 2020;24(1):65.doi:10.1186/s13054-020-2787-9.
- 95.**Piastra M, De Luca D, De Carolis MP, et al.Nebulized iloprost and noninvasive respiratory support for impending hypoxaemic respiratory failure in formerly preterm infants: A case series. *Pediatr Pulmonol* 2012;47:757-762.
- 96.**DiBlasi RM, Crotwell DN, Shen S, et al.Iloprost Drug Delivery during Infant Conventional and High-Frequency Oscillatory Ventilation.*Pulm Circ* 2016;6:63-69.
- 97.**Allan PF, Osborn EC, Chung KK, et al.High-Frequency Percussive Ventilation Revisited. *J Burn Care Res* 2010;31:510-520.
- 98.**Dumas De La Roque E, Bertrand C, Tandonnet O, et al.Nasal high frequency percussive ventilation versus nasal continuous positive airway pressure in transient tachypnea of the newborn: A pilot randomized controlled trial (NCT00556738): NHFPV Versus NCPAP in Transient Tachypnea of the Newborn.*Pediatr Pulmonol* 2011;46:218-223.
- 99.**Renesme L, Dumas de la Roque E, Germain C, et al.Nasal high-frequency percussive ventilation vs nasal continuous positive airway pressure in newborn infants respiratory distress: A cross over clinical trial.*Pediatr Pulmonol* 2020;55:2617-2623.
- 100.**Renesme L, Elleau C, Nolent P, et al.Effect of high-frequency oscillation and percussion versus conventional ventilation in a piglet model of meconium aspiration: Hi-Frequency vs. Conventional Ventilation in MAS.*Pediatr Pulmonol* 2013;48:257-264.
- 101.**Messier SE, DiGeronimo RJ, Gillette RK.Comparison of the Sensormedics® 3100A and Bronchotron® transporter in a neonatal piglet ARDS model.*Pediatr Pulmonol* 2009;44:693-700.

102.Rehan VK, Fong J, Lee R, et al.Mechanism of Reduced Lung Injury by High-Frequency Nasal Ventilation in a Preterm Lamb Model of Neonatal Chronic Lung Disease.

Pediatr Res 2011;70:462-466.

103.Null DM, Alvord J, Leavitt W, et al.High-frequency nasal ventilation for 21d maintains gas exchange with lower respiratory pressures and promotes alveolarization in preterm lambs.

Pediatr Res 2014;75:507-516.

Figure 1. Non-invasive high-frequency oscillatory ventilation (NHFOV) during spontaneous breathing in an active lung model of neonatal restrictive (model A) and mixed (model B) respiratory failure. Blue, green, red and orange lines, represents flow, volume, airway pressure (measured at the lung) and inspiratory muscle pressure (spontaneously generated by the patient), respectively.

Data have been generated using a bench model modified from adult setting consisting of a neonatal mannequin ventilated through a nasal mask and whose trachea had been connected to an electronic active test lung (ASL5000; Ingmar Medical, Pittsburgh, Pennsylvania, USA). A SensorMedics SM3100A oscillator (Vyair, San Diego, California, USA) was used. Data were filtered at 100 Hz and measured at the lung simulator using a specific software (ICU Lab rel.2.3; KleisTEK Advanced Electronic System, Bari, Italy). **Model A** mimics a preterm neonate with RDS (birth weight: 1.5 kg, resistances: 100 cmH₂O/L/s, compliance: 0.5 mL/cmH₂O/Kg, respiratory rate: 40 breaths/min, Paw: 8 cmH₂O, amplitude 30 cmH₂O; frequency 9 Hz, IT 50%). **Model B** mimics an infant with BPD and acute worsening of respiratory function (acute-on-chronic respiratory failure) (birth weight: 2 kg, resistances: 300 cmH₂O/L/s, compliance: 0.4 mL/cmH₂O/Kg, respiratory rate: 50 breaths/min, Paw: 10 cmH₂O, amplitude 50 cmH₂O; frequency 6 Hz, IT 50%); notice how the inspiratory effort is weaker in this example, as the patients is experiencing relevant work of breathing. A single spontaneous breath is shown in both panels. **Abbreviations:** Paw: airway pressure measured at the lung; Pmus: negative spontaneously generated inspiratory muscle pressure.

Table 1. Factors influencing gas exchange during NHFOV. Effect of interface is variable because different interfaces may facilitate or reduce oscillation transmission through an improved patients' comfort and/or changing pressure leaks and/or oscillation dampening. *Leaks are generally reducing gas exchange through decreased oscillation transmission, but moderate leaks have been demonstrated to increase CO₂ clearance under certain experimental conditions.^{37,38} The effects of P_{aw} or gravity are variable because increasing constant distending pressure, or positioning the infant prone or supine may change regional compliance and affect oscillation transmission.

Variable	Effect on gas exchange
Oscillation amplitude	↑
Inspiratory time	↑
Frequency	↓
Leaks	↓*
Interface	variable
Mean airway pressure	variable
Gravity (patient positioning)	variable

Table 2. Randomized clinical trials comparing NHFOV versus single level or bilevel CPAP.

Gestational age and prenatal steroids were considered as the weighted mean of the two trial arms.

Three studies had a crossover design;^{62,65,70} the remaining were parallel trials. Values have been rounded to the closest decimal. *Asterisks indicate that patients in trial arms have equivalent Paw.

Abbreviations: CPAP: continuous positive airway pressure; GA: gestational age; IMV: invasive mechanical ventilation; N.A.: not available; NARDS: neonatal acute respiratory distress syndrome; NHFOV: non-invasive high frequency oscillatory ventilation; PaCO₂: carbon dioxide levels; Paw: mean airway pressure; RDS: respiratory distress syndrome.

Author/year	N. of patients	GA (weeks)	Prenatal steroids (%)	Primary outcomes	Secondary outcomes	Maximum Paw and amplitude	Enrolled population
Bottino/2018 ⁶²	30	26.4	N.A.	PaCO ₂	N.A.	8/10*	Stable preterm neonates
Chen/2020 ⁶³	206	32.6	89.8	Need for IMV and PaCO ₂	Complications of prematurity	16/40	Preterm neonates with RDS or NARDS as post-extubation support
Iranpour/2019 ⁶⁴	68	33	26.4	Duration of CPAP or NHFOV	Need for re-intubation; Complications of prematurity	8/20*	Preterm neonates with RDS as primary support
Klotz/2018 ⁶⁵	26	26.7	100	PaCO ₂	Apneas, bradycardia and safety data	8/N.A.*	Stable preterm neonates
Lou/2017 ⁶⁶	65	32.4	38.4	Need for IMV	Oxygenation and PaCO ₂ , complications of prematurity	N.A.	Preterm neonates with RDS as post-extubation support

Lou/2018 ⁶⁷	65	33.8	35.3	Oxygenation and PaCO ₂	IMV duration, apneas, complications of prematurity	12/35	Preterm neonates with RDS as post-extubation support
Malakian/2018 ⁶⁸	124	31.1	53.9	Need for IMV	IMV duration, complications of prematurity	8/7*	Preterm neonates with RDS as primary support
Mukerji/2017 ⁶⁹	39	28.8	80.9	Feasibility	IMV duration, PaCO ₂ , complications of prematurity	10/ N.A.*	Preterm neonates with RDS as post-extubation support
Rüegger/2018 ⁷⁰	40	26.5	90	Bradycardia and/or desaturation	Vital parameters and safety data	7/40*	Stable extremely preterm neonates
Zhu/2017 ⁷¹	76	31.8	36.7	Need for IMV	Complications of prematurity	6/ N.A.*	Preterm neonates with RDS as post-extubation support
Zhu/2017 ⁷²	38	31.8	36.6	Oxygenation and PaCO ₂	Complications of prematurity	10/10*	Preterm neonates with RDS as post-extubation support

Figure 2. Meta-analysis of NHFOV trials: Forrest plots for the more commonly studied outcomes. Panel A and B show need for intubation and mechanical ventilation (681 patients) and PaCO₂ levels after NHFOV application (662 patients), respectively. NHFOV and the single level or biphasic CPAP are considered as treatment (Trt) and control (Ctrl) arm, respectively; events per arm and odds ratio or mean difference (95% confidence interval) are reported in panel A and B, respectively. Square size is proportional to trial weight. Diamond width indicates the 95% confidence interval of the final effect size. The need for intubation and invasive ventilation was considered at any timepoint after intervention (some trials defined this outcome within 72 hours, others within a 7-days time-window). PaCO₂ levels were considered at any timepoint after intervention (trials defined this outcome by measuring PaCO₂ at various times after the intervention). Trials weight for the outcome intubation were: Chen: 36.138%, Iranpour: 1.636%, Lou: 10.087%, Lou-2: 12.530%, Malakian: 9.406%, Mukerji: 8.153%, Zhu: 14.882%, Zhu-2: 7.167%. Trials weight for the outcome PaCO₂ levels were: Bottino: 10.820%, Chen: 11.968%, Iranpour: 11.454%, Klotz: 8.461%, Lou: 11.471%, Lou-2: 11.762%, Malakian: 11.740%, R uegger: 10.651%, Zhu-2: 11.672%. **Abbreviations:** 95% CI: 95% confidence interval; CPAP: continuous positive airway pressure; Ctrl: control arm (i.e.: single level or biphasic CPAP); NHFOV: non-invasive high frequency oscillatory ventilation; PaCO₂: carbon dioxide levels; Trt: treatment arm (i.e.: NHFOV).

Figure 3. Proposal for a tailored protocol to apply NHFOV in extremely preterm infants with developing BPD (i.e.: chronic pulmonary insufficiency of prematurity).⁸⁶ This is the protocol in use at Paris Saclay University Hospitals NICU. Different types of non-invasive respiratory techniques are used after the first week of life in extremely preterm infants if they experience a worsening of their respiratory function. NHFOV is integrated in the strategy with the other

techniques based on a physiology-driven approach. Hypoxic respiratory failure (blue lines) is defined with an increased work of breathing (Silverman score >4) without hypercarbia and with $FiO_2 > 0.4$ to achieve peripheral saturation between 90% and 95% and is treated with synchronized conventional non-invasive ventilations (NIV-NAVA or sNIPPV); NHFOV is used if these fail. Hypercapnic respiratory failure (red lines) is defined with hypercarbia ($CO_2 > 65$ mmHg) and acidosis ($pH < 7.20$), irrespective of the oxygenation deficit, and treated with NHFOV as first line. NHFOV is managed applying alveolar recruitment maneuvers and with a close multimodal monitoring. Definition criteria should be fulfilled for at least 4-6h before instigating NIV-NAVA, sNIPPV or NHFOV and patients are monitored overtime with several non-invasive techniques (see text for more details). As the patient is improving the respiratory support can be de-escalated. Full and hatched lines, indicate deterioration and improvement of respiratory conditions, respectively.

*The choice between NIV-NAVA and sNIPPV depends on the availability of ventilators.

Abbreviations: BPD: broncho-pulmonary dysplasia; CPAP: continuous positive airway pressure; EDIN: “*Echelle et Inconfort du Nouveau-né*” score; FiO_2 : inspired oxygen fraction; LUS: lung ultrasound score; NIV-NAVA: non-invasive ventilation with neurally adjusted ventilator assist; NHFOV: non-invasive high frequency oscillatory ventilation; PI: perfusion index; $SatO_2$: peripheral hemoglobin saturation; sNIPPV: synchronized non-invasive positive pressure ventilation; WOB: work of breathing.

Table 3. Suggested parameters boundaries of NHFOV for extremely preterm infants with developing BPD (i.e.: chronic pulmonary insufficiency of prematurity). These suggestions have been modified from those previously proposed,¹ based on accumulated clinical experience.

Inspiratory time should be fixed at 50%. Parameters may require serial adjustments according to

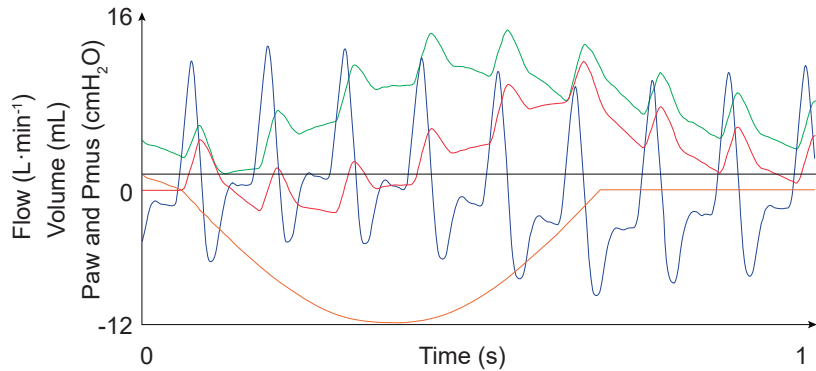
patients' monitoring. Paw should be titrated on oxygenation and/or ultrasound assessed lung aeration. Oscillation amplitude and frequency should be titrated according to transcutaneous CO₂ levels. Interfaces might also impact on the NHFOV performance and patients' comfort needing to be changed and requiring parameters adjustments.

	Minimum	Maximum
Mean airway pressure (cmH ₂ O)	10	18
Amplitude (cmH ₂ O)	30	55
Frequency (Hz)	8	12

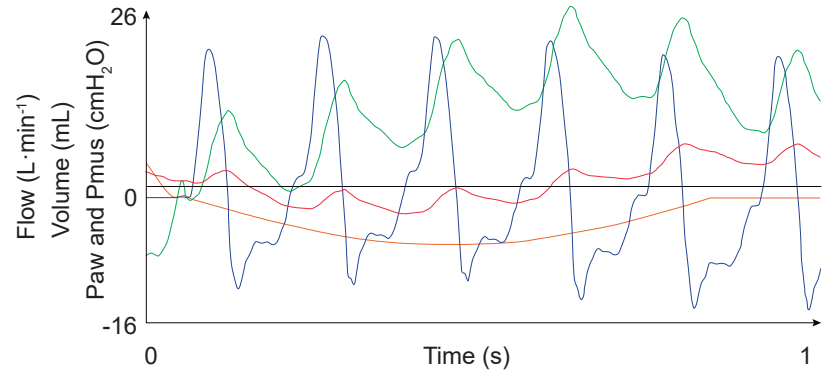
Data from Steinhorn R, Davis JM, Göpel W, et al. Chronic Pulmonary Insufficiency of Prematurity: Developing Optimal Endpoints for Drug Development. *J Pediatr* 2017;191:15-21.e1.

Figure 4. Illustrative time-pressure waveform during neonatal NHFPV. Conventional breaths are drawn with superimposed percussions. Ventilatory parameters to be decided by clinicians are indicated in the figure. Pressure rates for conventional breaths and flow rate for the pulsatile percussions must also be set to decide the maximum delivered pressures. **Abbreviations:** ET: conventional breath expiratory time; i/e ratio: inspiratory/expiratory ratio for the gas percussions; IT: conventional breath inspiratory time; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure.

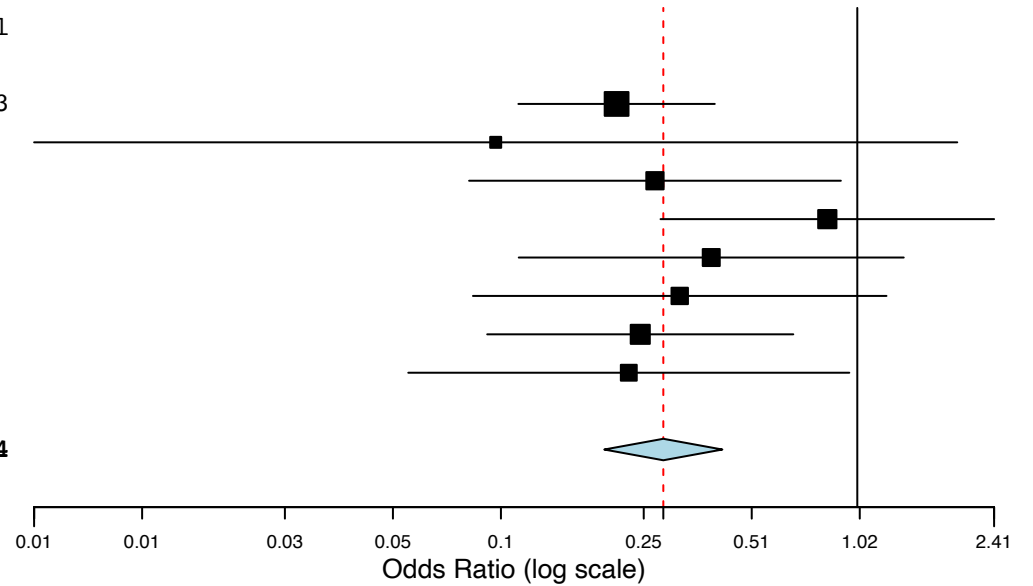
A



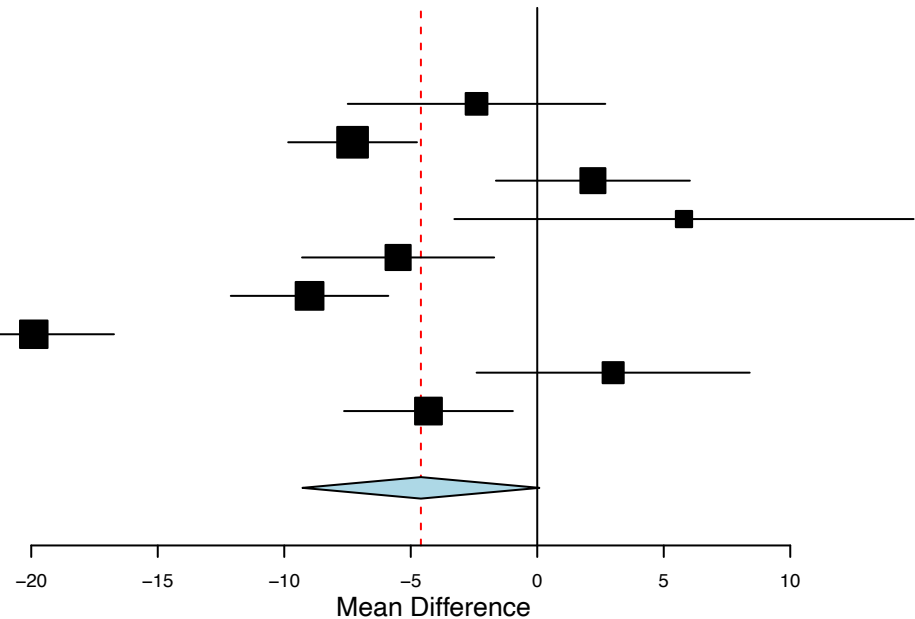
B

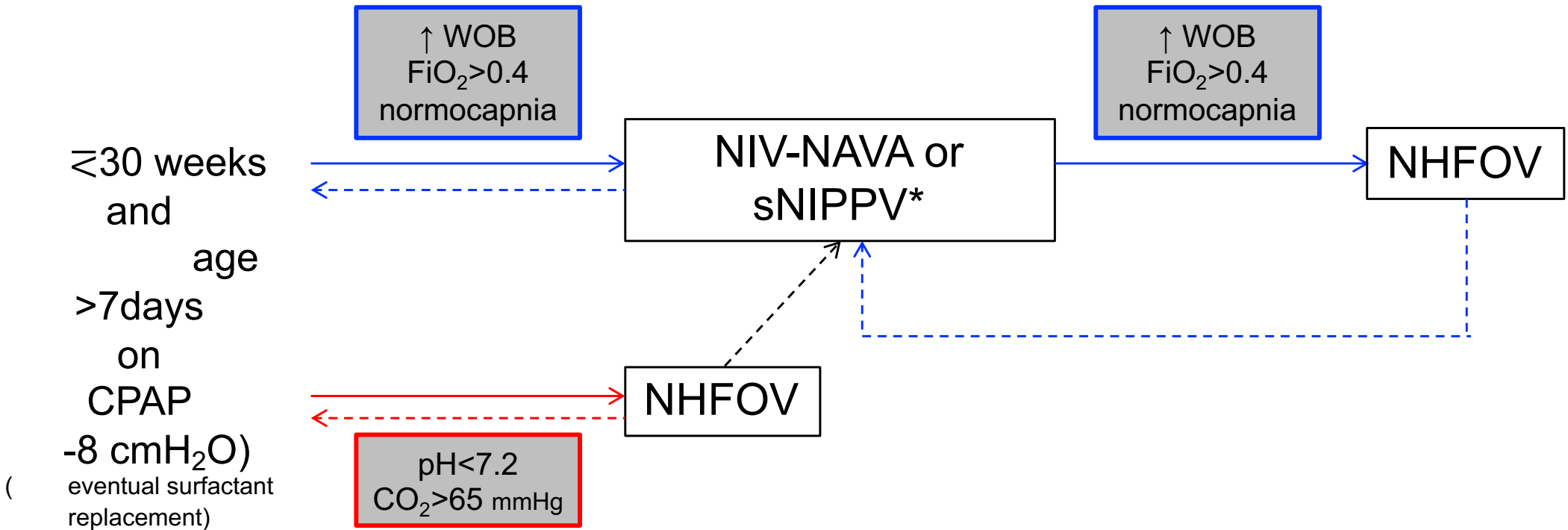


Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Chen 2020	0.213 (0.114, 0.401)	19/103	53/103
Iranpour 2019	0.098 (0.005, 1.900)	0/34	4/34
Lou 2017	0.273 (0.083, 0.900)	5/34	12/31
Lou-2 2018	0.825 (0.283, 2.406)	9/33	10/32
Malakian 2018	0.392 (0.114, 1.347)	4/63	9/61
Mukerji 2017	0.320 (0.085, 1.206)	6/16	15/23
Zhu 2017	0.248 (0.093, 0.663)	9/37	22/39
Zhu-2 2017	0.231 (0.056, 0.950)	4/17	12/21
Overall (I²=0 % , P=0.594)	0.288 (0.197, 0.421)	56/337	137/344



Studies	Estimate (95% C.I.)
Bottino 2018	-2.400 (-7.489, 2.689)
Chen 2020	-7.300 (-9.845, -4.755)
Iranpour 2019	2.200 (-1.633, 6.033)
Klotz 2018	5.800 (-3.276, 14.876)
Lou 2017	-5.500 (-9.296, -1.704)
Lou-2 2018	-9.000 (-12.113, -5.887)
Malakian 2018	-19.900 (-23.069, -16.731)
Ruegger 2018	3.000 (-2.397, 8.397)
Zhu-2 2017	-4.300 (-7.636, -0.964)
Overall (I²=9267 % , P<0.001)	-4.599 (-9.280, 0.082)





overtime (LUS score, transcutaneous blood gases, EDIN and COMFORT score, SatO₂ and PI)

