In The Name of God

Challenges of early non-invasive ventilation (N-CPAP) in newborns

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We are living today in a new era in respiratory support of the sick and immature neonate.

Postnatal respiratory support should not interfere with the physiological changes that occur naturally in the lungs at birth and early hours of life.

In the past decade, there has been an increased understanding of respiratory physiologic changes during fetal-to-neonatal transition, which could be used to improve respiratory support in the delivery room (DR) and after birth.

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PHYSIOLOGIC CHANGES AFTER BIRTH:

-Clearance of Lung Liquid

١- airway liquid clearance
٢- liquid accumulation within the lung's interstitial tissue compartment
٣- respiratory gas exchange and metabolic homeostasis

-Gas Exchange

-Crying and Breathing

To establish FRC, preterm infants use different breathing patterns including normal breathing, crying, grunting, expiratory breaking, and panting.

-Opening and Closure of Glottis/Epiglottis

-Trigemino-cardiac Reflex

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Because nasal CPAP/noninvasive ventilation (NIV):

-facilitates lung expansion and formation of a functional residual capacity (FRC)

-mitigates lung injury by avoiding baro-volu-rheo-Bio-atelecto trauma and

-compatibility with PHYSIOLOGIC CHANGES AFTER BIRTH

has gradually emerged as the first choice of respiratory support in preterm neonates.

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The types of non-invasive respiratory support:

Non-invasive Non-cycled:

*Continous positive Airway Pressure(CPAP): Continous-Flow CPAP (CF-CPAP) & Variable-Flow CPAP (VF-CPAP)
* Heated Humidified High-Flow Nasal Cannula (HHHFNC)

Non-invasive cycled:

*Nasal Intermittent Positive Pressure Ventilation (NIPPV): Non-synchronized NIPPV (ns-NIPPV) & Synchronized NIPPV (s-NIPPV)
*Bi-level Positive Airway Pressure Nasal Bi-level Positive Airway Pressure (n-BiPAP) & Synchronized Bi-level Positive Airway Pressure (n-SiPAP)

Other:
* Nasal High-Frequency Oscillatory Ventilation (n-HFOV)
* Nasal Neurally Adjusted Ventilatory Assist (n-NAVA)

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the use of these methods of noninvasive respiratory support in preterm infants:

- for primary care (within the first ۶ hours of age) especially in preterm infants with RDS
- after Extubation
- Apnea of Prematurity

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CPAP is a form of NON-INVASIVE and NON-CYCELED ventilation

History:

١٩١٢ - Maintenance of lung expansion during thoracic surgery (S.Brunnel)

١٩٣٧ - High altitude flying to prevent hypoxemia (Barach et al)

١٩۶٧ - CPPB + IPPV to treat ARDS (Ashbaugh et al)

١٩٧١ - Term CPAP introduced, used to treat HMD in neonates (Gregory et al)

١٩٧٢ - CPAP used to treat ARF (Civetta et al)

١٩٧٣ - CPAP used to treat COPD (Barach et al)

١٩٨٢ - Modern definition of CPAP (Kielty et al)

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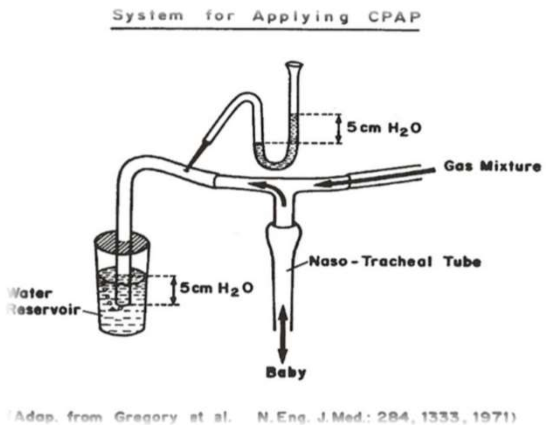

Schematic representation of the system used for applying continuous positive airway pressure
(adapted from Gregory, et al.)

The New England Journal of Medicine

Volume 284 JUNE 17, 1971 Number 24

TREATMENT OF THE IDIOPATHIC RESPIRATORY-DISTRESS SYNDROME WITH CONTINUOUS POSITIVE AIRWAY PRESSURE*

George A. Gregory, M.D., Joseph A. Kitterman, M.D., Roderic H. Phibbs, M.D., William H. Tooley, M.D., and William K. Hamilton, M.D.

Abstract We applied a continuous positive airway pressure to 20 infants (birth weight 930 to 3800 g) severely ill with the idiopathic respiratory-distress syndrome. They breathed spontaneously. Pressure, up to 12 mm of mercury, was delivered through an endotracheal tube to 18 infants and via a pressure chamber around the infant's head to two. Arterial oxygen tension rose in all, permitting us to lower the inspired oxygen an average of 37.5 per cent within 12 hours. Minute ventilation decreased with increased continuous positive airway pressure, but this had little effect on arterial carbon dioxide tension, pH, arterial blood pressure and lung compliance. Sixteen infants survived, including seven of 10 weighing less than 1500 g at birth.

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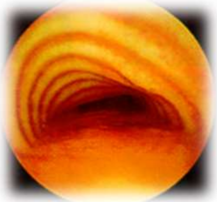
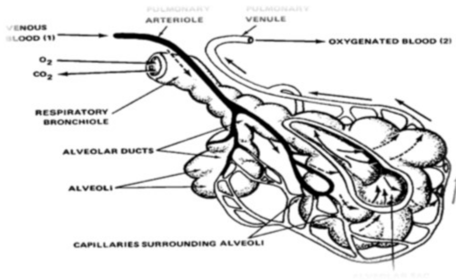
CPAP applies his effects in the following ways:



۱.Decrease airway resistant

۲.Decrease obstructive apnea

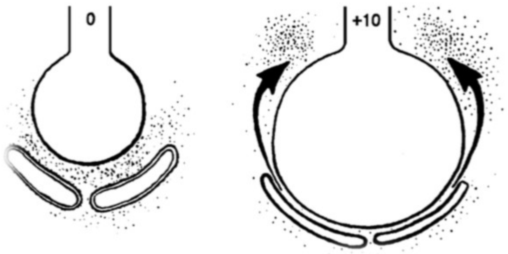


۳.Decrease alveolar edema

۴.Protective effect on surfactant and surfactant release may be enhanced by CPAP in RDS

۵. both inspiratory and expiratory times are increased with CPAP

۶.Redistribution of lung water



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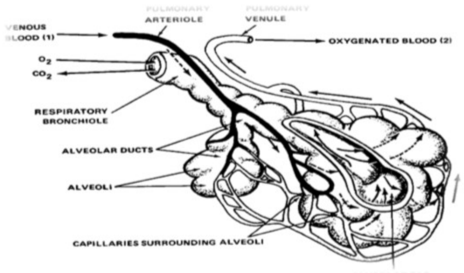
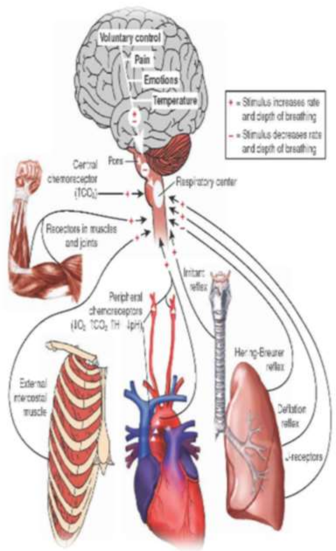


٧.Increase FRC

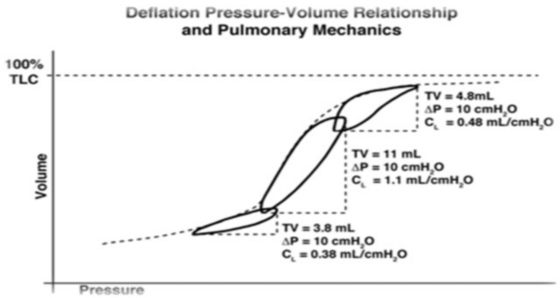
٨.Improve oxygenation and to lesser extent PaCO٢ (washout effect)

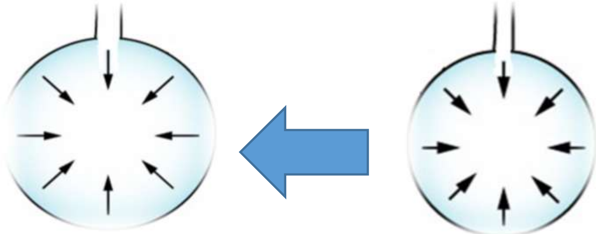


٩.Decrease of Respiratory Rate Due to hering-Breuer Reflex

١٠. Increases the end-expiratory lung volume and Annihilation of grunting

١١.Decrease of Respiratory Effort(P = ٢T/r)





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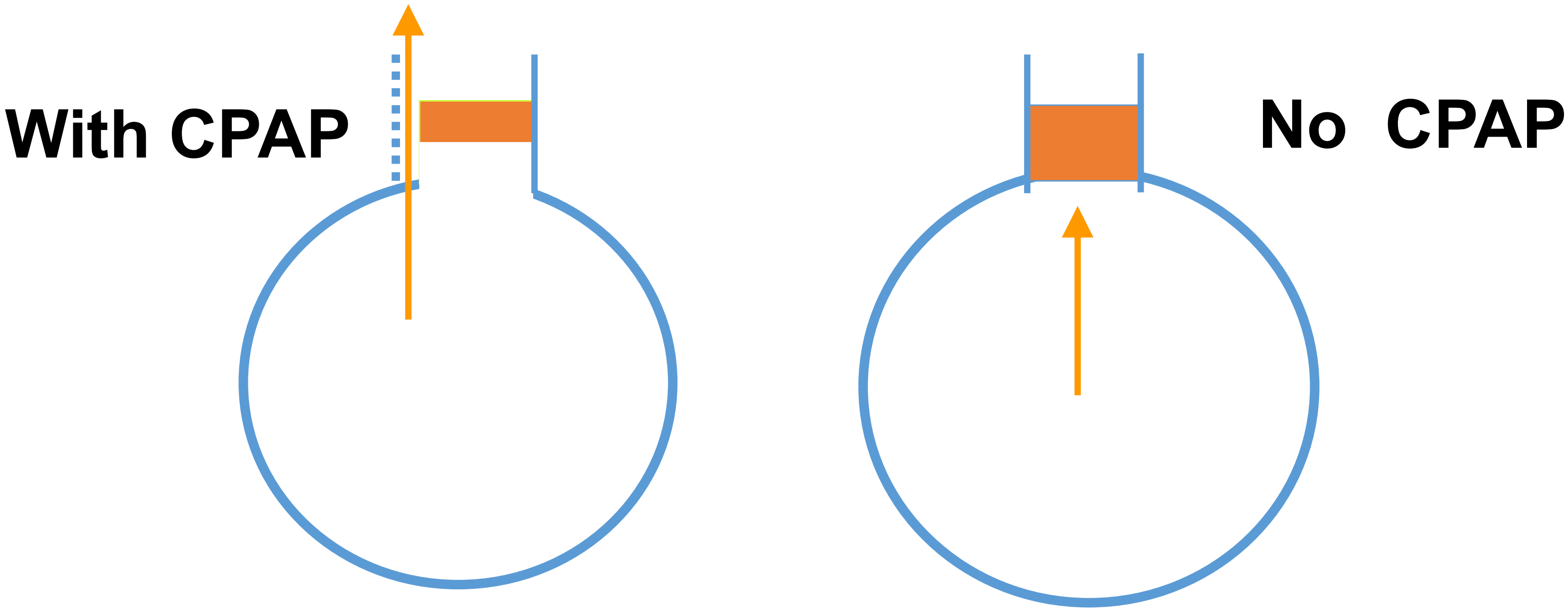
۱۲.Epicene of check-valve mechanism



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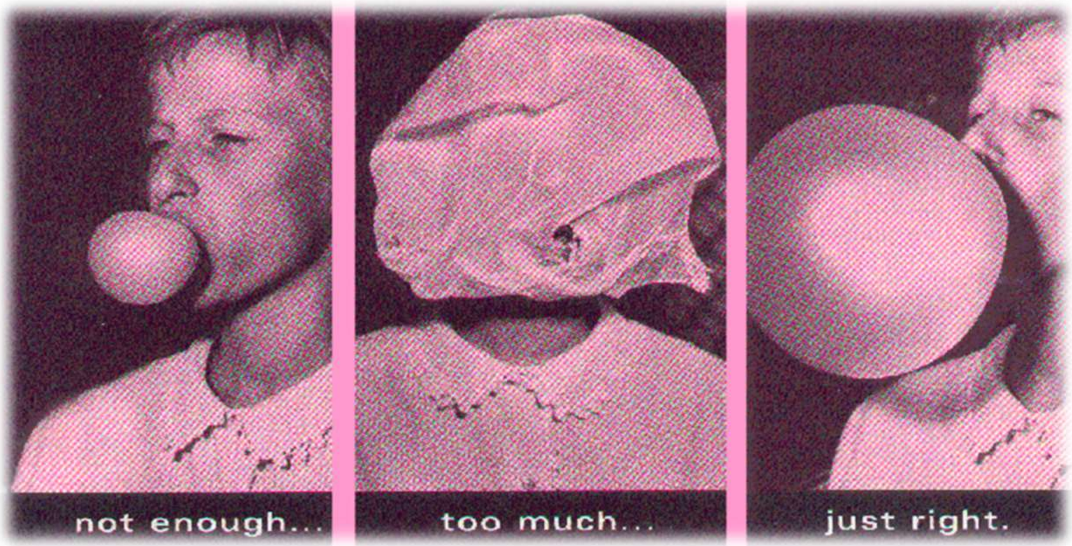
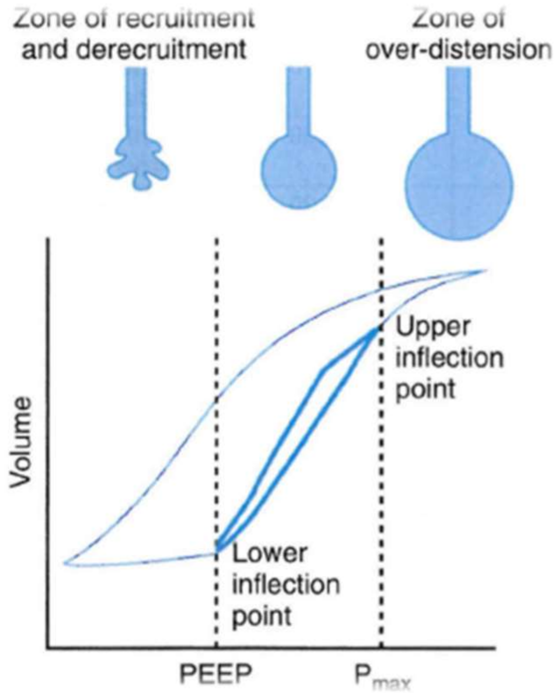
GOAL OF CPAP

achieve the lowest possible pressure to maintain open alveoli without overdistention





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Components of CPAP System

- Flow generator (Ventilator or flow derive device)
- A circuit for continuous flow of inspired gas (Blender, Flow-meter, Heated humidifier and tube)
- A mean of creating positive pressure in the circuit (injector)

Expiratory flow valve (e.g ventilator)
Underwater bubble CPAP (Hudson CPAP)
Injector

- A device to connect the circuit to the patient's airways (e.g. Nasal prong)

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The meta-analysis of studies conducted **before routine application of CPAP** demonstrated a lower *mortality rate* (relative risk [RR] ۰.۶۹; ۹۵% confidence interval [CI] ۰.۵۶–۰.۸۵; number needed to benefit [NNTB] ۲۰) and a decrease in the risk of *air leak* (RR ۰.۷۹; ۹۵% CI ۰.۶۳–۰.۹۸) in preterm infants receiving prophylactic surfactant versus rescue surfactant.

Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. ۲۰۰۱;(۲): CD۰۰۰۵۱۰.

However, **when the studies that allowed for routine application of CPAP were included in the meta-analysis** (National Institute of Child Health and Human Development SUPPORT Trial and Vermont Oxford Network Delivery Room Management Trial), the benefits of prophylactic surfactant on mortality (RR ۰.۸۹; ۹۵% CI ۰.۷۶–۱.۰۴) and air leak (RR ۰.۸۶; ۹۵% CI ۰.۷۱–۱.۰۴) could no longer be demonstrated.

Furthermore, infants receiving prophylactic surfactant had a higher incidence of BPD or death than did infants stabilized on CPAP (RR ۱.۱۲; ۹۵% CI ۱.۰۲–۱.۲۴).

Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. ۲۰۱۲;۳(۳):CD۰۰۰۵۱۰.

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۱۰-۱۵ years after these initial descriptions, several large multicenter randomized trials of respiratory management after birth compared an initial strategy of early CPAP with immediate intubation and surfactant administration.

۱.The CPAP Or INtubation at Birth **(COIN)**

Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. ۲۰۰۸; ۳۵۸:۷۰۰–۸. [PubMed: ۱۸۲۷۲۸۹۳].

۲. The Surfactant Positive Pressure and Oxygen Randomized Trial **(SUPPORT)**

Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. ۲۰۱۰; ۳۶۲:۱۹۷۰–۹. [PubMed: ۲۰۴۷۲۹۳۹].

۳.and last the **Vermont Oxford Network** delivery room management trial, in the Vermont Oxford Network trial, Dunn et al.

Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al. Randomized trial comparing ۳ approaches to the initial respiratory management of preterm neonates. Pediatrics. ۲۰۱۱; ۱۲۸:e۱۰۶۹–۷۶. [PubMed: ۲۲۰۲۵۵۹۱].

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Another study is **CURPAP**

The CURPAP trial aimed to evaluate the efficacy of combining prophylactic surfactant and early nasal CPAP in very preterm infants and enrolled ۲۰۸ infants born at ۲۵ and ۰ / ۷–۲۸ and ۶ / ۷ weeks

Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics ۲۰۱۰; ۱۲۵: e۱۴۰۲–۹.

Conclusions:

Prophylactic surfactant was not superior to n-CPAP and early selective surfactant in decreasing the need for MV in the first ۵ days of life and the incidence of main morbidities of prematurity in spontaneously breathing very preterm infants on n-CPAP.

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Based on these findings, the **American Academy of Pediatrics Committee on Fetus and Newborn** subsequently published a policy statement concluding that:

"Early initiation of CPAP with subsequent selective surfactant administration in extremely preterm infants results in lower rates of BPD/death when compared with treatment with prophylactic surfactant therapy" (LOE ۱)

"When compared with prophylactic or early surfactant therapy, early use of CPAP, coupled with subsequent selective use of surfactants, results in reduce the duration of mechanical ventilation and postnatal corticosteroid therapy" (LOE ۱)

COMMITTEE ON FETUS AND NEWBORN. Respiratory support in preterm infants at birth. Pediatrics. ۲۰۱۴; ۱۳۳:۱۷۱–۴. [PubMed: ۲۴۳۷۹۲۲۸].

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Recommendations of European Consensus Guidelines on the Management of Respiratory Distress Syndrome – ۲۰۱۹ Update

"CPAP should be started from birth in all babies at risk of RDS, such as those < ۳۰ W gestational age who do not need intubation for stabilization"

Quality of evidence: A (High quality)

Strength of recommendation: ۱ (Strong recommendation for using intervention)

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Despite the fact that early CPAP and selective surfactant therapy is preferable based on the studies conducted up to now, there are fundamental challenges in various fields of non-invasive respiratory support:

**Which type of non-invasive support should we use?*
**Non-invasive respiratory support with which type of flow generation source is most effective?*
**Non-invasive respiratory support with which type of pressure generation mechanism is more effective?*
**Non-invasive respiratory support with which type of interface is more effective?*
**What is the best position for a baby under non-invasive respiratory support?(supine or prone)*
**At what level of pressure is non-invasive respiratory support more effective?*
**What is the best method of weaning from non-invasive respiratory support?*
**The challenges that exist in nursing and supportive care in newborn under non-invasive respiratory support*
**The challenges of using non-invasive respiratory support in resource limited settings*
**The challenge is to combine studies that address a specific clinical question and have similar characteristics in terms of populations, interventions, comparators, and outcomes, so that their combined results provide a more precise estimate of the effect that can be validly extrapolated into clinical practice*

And …………

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Which type of non-invasive support should we use?

Despite widely spread use of non-invasive respiratory support and an expansion of methods to achieve it, there is often a paucity of evidence to determine which method is most effective and are being tested in clinical trials.

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HHHFNC and mechanism of action

<u>provision of a distending pressure</u> which contributes to developing and maintaining FRC and airway patency

increases average airway pressure by ۰.۸ cm $H_{۲}O$ for each ۱ L/min increase in flow

fluctuations of airway pressure (although not clinically relevant) and observed that during HFNC (for ۶ L/min of flow) only ۷۵% of infants reached a pressure of ۴ cm $H_{۲}O$ and values greater than ۵ cm $H_{۲}O$ were rarely achieved.

Liew Z, Fenton AC, Harigopal S, et al. Physiological effects of high-flow nasal cannula therapy in preterm infants. Arch Dis Child Fetal Neonatal Ed ۲۰۲۰; ۱۰۵(۱):۸۷–۹۳.

Sreenan et al demonstrated that flow rates of ۱ to ۲.۵ L/min via NC generated end-distending pressure similar to CPAP at ۶ cm $H_{۲}O$. The flow needed to generate the end-distending pressure was proportional to the size of the prong and gestational age of newborn.

Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. Pediatrics. ۲۰۰۱; ۱۰۷:۱۰۸۱–۱۰۸۳. [PubMed: ۱۱۳۳۱۶۹۰].

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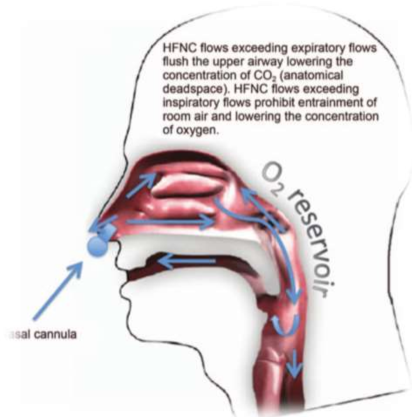
<u>wash out upper airways,</u> which leads to a reduction of the physiologic dead space as suggested by the decrease of patient's respiratory rate and PaCO۲ and by the improvement of oxygenation.

**double prong HFNC had a greater impact on O۲,*
**whereas single prong HFNC had a greater impact on CO۲ elimination*



Reduces the metabolic cost of **<u>gas conditions</u>** by providing air with ۱۰۰% relative humidity.

improves **<u>airway conductance</u>** by reducing the effect of cold air.

The greatest effect of HHHFNC is caused by these last ۳ mechanisms rather than the first mechanism

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the **American Academy of Pediatrics** did not recommend HFNC as primary respiratory support for preterm infants with RDS, which is in line with a **European Consensus** of experts who suggest that "At present, CPAP remains the preferred initial method of non-invasive support."

the **American Academy of Pediatrics** concluded that HFNC "may be an effective alternative to n-CPAP for post-extubation failure," in agreement with the **European Consensus** of experts, which reports that "During weaning, HFNC can be used as an alternative to CPAP for some babies.

Uchiyama A, Okazaki K, Kondo M, et al. Randomized controlled trial of high-flow nasal cannula in preterm infants after extubation. Pediatrics ۲۰۲۰;۱۴۶(۶): e۲۰۲۰۱۱۰۱.

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Clinics in Perinatology ۴۸ (۲۰۲۱)

For primary respiratory support:

o On the basis of current literature, n-CPAP should remain the first-choice in preterm infants with RDS, especially in very preterm infants.

o HFNC, however, is an appropriate therapy for moderately preterm infants with signs of mild to moderate respiratory distress, especially when rescue CPAP is not available.

For weaning from invasive ventilatory support:

o In the post-extubation phase, HFNC is as effective as n-CPAP (in term of risk of re-intubation, mortality, and BPD or mortality) for babies >۲۸ weeks' gestation, although there is less evidence for smaller babies.

o Because it is also associated with decreased risk of nasal trauma at flow rates up to ۸ L/minute, this mode can represent an effective alternative in the weaning phase of RDS. Caution is recommended in extremely preterm infants.

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NIPPV

non-synchronized NIPPV

- elicit active expiratory efforts against the ventilator cycle
- delay spontaneous exhalation
- and therefore, delay the onset of the next inspiration
- may also activate laryngeal closure

Synchronized NIPPV

- positive pressure is transmitted efficiently to the lungs because it is delivered when the glottis is opening, with consequent reduced risk of abdominal distension
- there is an effective increase in the trans-pulmonary pressure produced by the sum of negative pressure from the patient and positive pressure from the ventilator
- synchronized mechanical pressure waves stabilize the chest wall of the premature infant during the inspiratory phase

Triggering devices to synchronize noninvasive ventilation :

-Abdominal pneumatic or Graseby capsule
-Pressure triggering
-Flow triggering
-NAVA trigger

Challenge:
Witch types of triggering is better?

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meta-analysis aimed to compare the efficacy of NIPPV versus CPAP:
***Clinics in Perinatology* ۴۸ (۲۰۲۱).**

***Primary respiratory support**

۱۸ trials and ۱۹۰۰ infants + ۸ newly published trials comprising ۸۵۰ infants

***Post-extubation respiratory support**

Fifteen trials enrolling ۲۴۴۴ infants were included + Data from ۵ trials published between ۲۰۱۶ and ۲۰۲۰ enrolling ۱۰۱۳ infants

These findings are consistent with those of the corresponding ۲۰۱۶ Cochrane Review.
Lemyre B, Laughon M, Bose C, et al. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. Cochrane Database Syst Rev ۲۰۱۶;۱۲(۱۲):CD۰۰۵۳۸۴.

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Non-synchronized type should not be used for respiratory support especially in babies who have apnea

Because:

the majority of non-synchronized pressure peaks occur during spontaneous expiration and do not contribute to tidal volume and When the pressure rises coincided with spontaneous inspiration, only a ۱۵% increase in relative tidal volume was noted.

any advantage of non-synchronized NIPPV may arise from a higher MAP rather than from the effect of the intermittent pressure peaks themselves.

Another important consideration is the quality of the patient's comfort during ventilation: Setting a rate of ۲۰ to ۴۰ cycles/min on the ventilator means that ۲۸,۸۰۰ to ۵۷,۶۰۰ pressure waves will be delivered to the infant through the interface every day and most of them will be asynchronous.

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For Synchronized NIPPV Physiologic and clinical positive effects are currently widely demonstrated and recommended for <u>PRIMARY MODE OF VENTILATION</u> (supplemental oxygen, hospital stay, duration of MV, incidence of bronchopulmonary dysplasia), <u>AFTER EXTUBATION</u> and <u>APNOEA OF PREMATURITY</u>

Tabacaru CR, Moores RR Jr, Khoury J, et al. NAVA-synchronized compared to nonsynchronized noninvasive ventilation for apnea, bradycardia, and desaturation events in VLBW infants. Pediatr Pulmonol ۲۰۱۹;۵۴:۱۷۴۲–۶.

Santin R, Brodsky N, Bhandari V. A prospective observational pilot study of synchronized nasal intermittent positive pressure ventilation (SNIPPV) as a primary mode of ventilation in infants > or ۵۲۸ weeks with respiratory distress syndrome (RDS). J Perinatol ۲۰۰۴;۲۴:۴۸۷–۹۳.

Lee BK, Shin SH, Jung YH, et al. Comparison of NIV-NAVA and NCPAP in facilitating extubation for very preterm infants. BMC Pediatr ۲۰۱۹;۱۹:۲۹۸.

Tabacaru CR, Moores RR Jr, Khoury J, et al. NAVA-synchronized compared to nonsynchronized noninvasive ventilation for apnea, bradycardia, and desaturation events in VLBW infants. Pediatr Pulmonol ۲۰۱۹;۵۴:۱۷۴۲.

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SNIPPV is superior to CPAP

- **as primary mode for RDS:**
  - o decrease need for invasive ventilation

- **as post-extubation mode:**
  - o decrease extubation failure
  - o decrease incidence of BPD

For both indications, ventilator-generated, synchronized NIPPV is most effective to prevent respiratory failure. Superiority of ventilator-generated NIPPV over flow-driver-generated NIPPV is explained by higher peak pressures used during ventilator-generated NIPPV.

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Challengs:

-Results show no reduction in mortality overall or within subgroups, irrespective of whether primary or post-extubation S-NIPPV support is delivered.

-Additional data from adequately powered RCTs are warranted to determine the benefits of S-NIPPV in smaller and more immature infants.

-A particular focus should be placed on long-term respiratory function following prolonged S-NIPPV use.

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-there are few large randomized controlled trials to compare the effectiveness of NCPAP and NIPPV as the primary respiratory support after birth and before surfactant administration.

the **NIV-MISA-RDS trial** An ongoing study and will provide clinical data for the selection of the initial non-invasive ventilation mode in preterm infants with a gestational age of <۳۰ weeks with spontaneous breaths after birth.

this trial to test the hypothesis that NCPAP is not inferior to NIPPV as the initial respiratory support in reducing the use of IMV in premature infants who have spontaneous breaths after birth and who do not require intubation in the first ۲ h after birth.

If MAPs were matched across all devices and all modes, there may be little difference between CPAP, flow-driver-generated NIPPV, and ventilator-generated NIPPV.

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European Consensus Guidelines on the Management of RDS ۲۰۱۹ Update

There is insufficient evidence to recommend synchronized NIPPV as primary mode of respiratory support in the delivery room.

It is not recommended to delay surfactant administration by escalating therapy from NCPAP to NIPPV.

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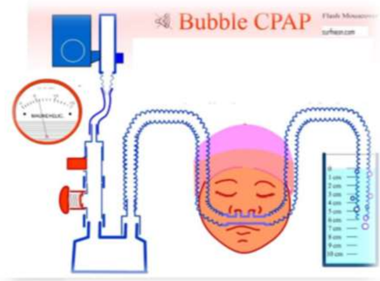
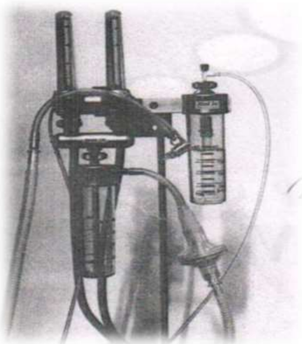
which type of flow generation source is most effective?

Ventilator derived CPAP (Expiratory flow valve)
Underwater bubble CPAP (Hudson CPAP)
Flow derived CPAP





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It has been reported that during bubble CPAP pressure oscillations occur able to generate volumes similar to those generated by high frequency oscillatory ventilation this might enhance gas exchange and promoted airway patency and improved physiological outcomes for premature neonates with RDS.

Pillow JJ, Hillman N, Moss TJ, Polglase G, Bold G, Beaumont C, Ikegami M, Jobe AH. Bubble continuous positive airway pressure enhances lung volume and gas exchange in preterm lambs. Am J Respir Crit Care Med. ۲۰۰۷; ۱۷۶:۶۳–۶۹. [PubMed: ۱۷۴۳۱۲۲۳].

In an attempt to support or refute these issues, Blackson et al evaluated BCPAP in vitro and in vivo to determine a physiological basis for ventilation augmentation.

Blackson T, Sherman TI, Touch SM, Cox T, Shaffer TH. Bubble continuous positive airway pressure (BCPAP) does not augment ventilation. Pediatr Res. ۲۰۰۳; ۵۳:۳۶۰A.

this study showed that BCPAP at ۱۰ L/min provides an HFOV effect that is measurable both in vitro and in vivo, and the bubble frequency is in the same frequency domain as commercial high frequency oscillatory ventilators.

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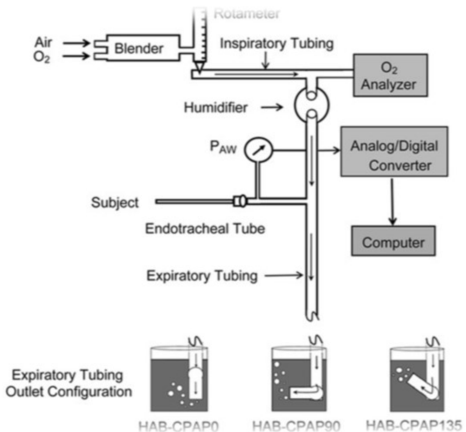
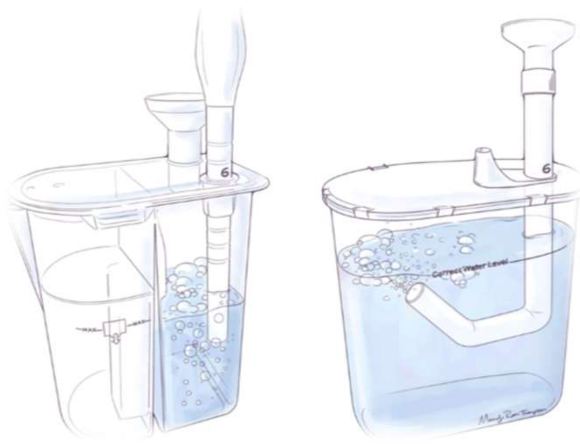
<u>High-amplitude BCPAP (HAB-CPAP)</u> provides high-frequency oscillations in the airway with higher amplitude by increasing the angle of gas entry at the water seal.

Using this device were able to demonstrate an increase in PaO۲ and a decrease in the work of breathing in an animal model of non-invasive respiratory support.

Diblasi RM, Zignego JC, Tang DM, Hildebrandt J, Smith CV, Hansen TN, Richardson CP. Noninvasive respiratory support of juvenile rabbits by high-amplitude bubble continuous positive airway pressure. Pediatr Res. ۲۰۱۰; ۶۷:۶۲۴–۶۲۹. [PubMed: ۲۰۳۰۸۹۴۰].





B.Barekatain

At greater angles, the oscillations were predominantly at lower dominant frequencies that allowed more time for volume delivery.

For HAB-CPAP, the authors postulate these mechanisms will improve alveolar recruitment.

Sturtz WJ, Touch SM, Locke RG, Greenspan JS, Shaffer TH. Assessment of neonatal ventilation during high-frequency oscillatory ventilation. Pediatr Crit Care Med. ۲۰۰۸; ۹:۱۰۱–۱۰۴. [PubMed: ۱۸۴۷۷۹۲۲].

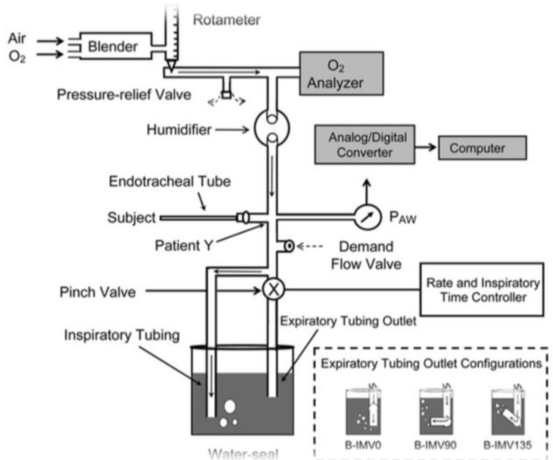
Further studies are warranted to demonstrate the safety and efficacy of this mode of ventilation in clinical settings

B.Barekatain

The bubble intermittent mandatory ventilator (B-IMV) is a simple, constant-flow device that allows spontaneous breathing in conjunction with timed (unsynchronized) positive pressure inflations.

The Paw control system consists of two conduits downstream of the patient interface, separated by a pinch valve that directs system gas to exit through water seals set at different depths. With the pinch valve closed, the depth in water of the deeper conduit determines the peak inspiratory pressure (PIP) of the subject.

With the pinch valve open, the gas flow selectively proceeds toward the shallower conduit, where the depth, and therefore backpressure, determines the positive end-expiratory pressure (PEEP).



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In animals study exhibited no differences in PaO_2 levels during support with CMV, B-IMV۰, B-IMV۹۰, and B-IMV۱۳۵.

However, $PaCO_2$ levels of animals ventilated on B-IMV۱۳۵ were lower than when managed on the other three modes of ventilation

ROBERT M. DIBLASI, JAY C. ZIGNEGO et al. Effective Gas Exchange in Paralyzed Juvenile Rabbits Using Simple, Inexpensive Respiratory Support Devices International Pediatric Research Foundation.Vol. ۶۸, No. ۶, ۲۰۱۰.

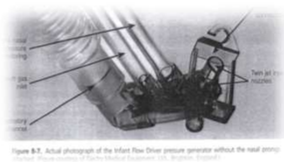
Further studies are warranted to demonstrate the safety and efficacy of this mode of ventilation in clinical settings

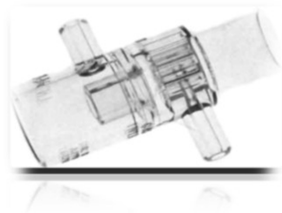
B.Barekatain

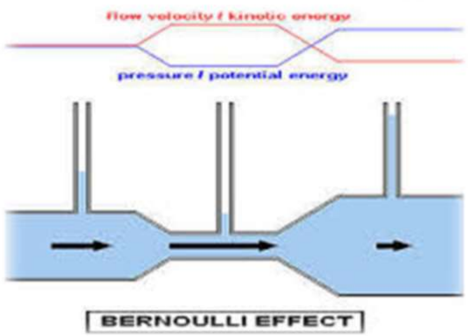
which type of pressure generation mechanism is more effective?

-Expiratory flow valve in ventilator derived CPAP
-Underwater valve in bubble CPAP
-Injector in flow derived CPAP (***Bernoulli effect during inspiration***)

infant flow system (IFD or aladdin system)
Arabella system
sensormedics cpap generator
Medijet system
benveniste gas-jet valve







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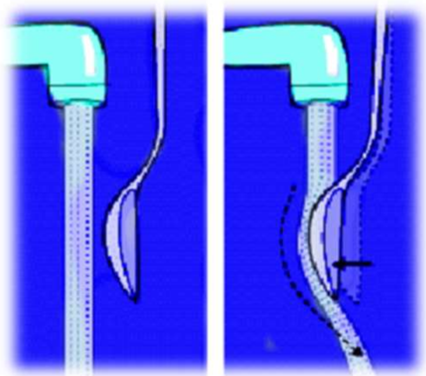
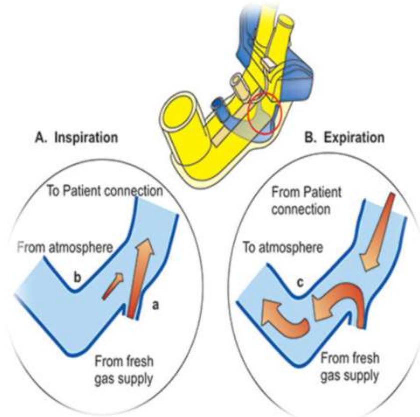
Continous flow CPAP (ventilator derived CPAP & bubble CPAP) vs Variable flow CPAP (Flow derived CPAP & Injector)

the ***Coanda effect*** (fluidic flip of inhaled air into the expiratory limb) during expiration maintain stable CPAP throughout the respiratory cycle

Variable-flow CPAP vs Continous-flow CPAP:

o decreases the WOB (in one study: to a quarter)
o maintain a more stable pressure level
o increases more significantly lung compliance
o allows a greater lung recruitment





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CF-CPAP is inferior to VF-CPAP (RR ۱.۴۱; ۹۵% CI ۱.۰۱–۱.۹۳) in preventing extubation failures.

Ramaswamy VV, Bandyopadhyay T, Nanda D, et al. Efficacy of noninvasive respiratory support modes as postextubation respiratory support in preterm neonates: a systematic review and network meta-analysis. Pediatr Pulmonol. ۲۰۲۰;۵۵:۲۹۲۴–۳۹.

On comparison with Bubble CPAP in preterm neonates with RDS and a gestational age less than ۳۲ wk, VF-CPAP was noted to have similar CPAP failure rates.

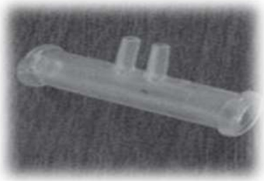
Bhatti A, Khan J, Murki S, Sundaram V, Saini SS, Kumar P. Nasal jet-CPAP (variable flow) versus bubble-CPAP in preterm infants with respiratory distress: an open label, randomized controlled trial. J Perinatol. ۲۰۱۵;۳۵:۹۳۵–۴۰.

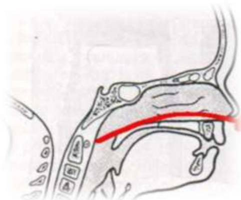
- Available data are inconsistent about physiologic and clinical effects of variable- flow vs. continuous- flow (bubble) CPAP
- More studies are needed to investigate the effect of different types of injectors

B.Barekatain

which type of interface is more effective?

Common interfaces used in the delivery room (DR) to provide NIV support are
-round and anatomical mask
-single or bi-nasal nasopharyngeal prongs
-bi-nasal prongs
-nasal mask
-RAM nasal cannula (NC) (Neotech RAM Nasal Cannula R , Neotech Products, Valencia, California, USA)





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for **primary neonatal resuscitation in the DR**

In a randomized, controlled trial, use of NC vs. face mask in more mature neonates (mean GA ۳۶ weeks), NC use resulted in significantly less need for intubation (۰.۶ vs. ۶.۳%; p < ۰.۰۰۱) and chest compressions (۱.۶۵ vs. ۸.۲۸%; p = ۰.۰۰۱) in the NC group.

Capasso L, Capasso A, Raimondi F, Vendemmia M, Araimo G, Paludetto R. A randomized trial comparing oxygen delivery on intermittent positive pressure with nasal cannulae versus facial mask in neonatal primary resuscitation. Acta Paediatr. (۲۰۰۵) ۹۴:۱۹۷–۲۰۰. doi: ۱۰.۱۰۸۰/۰۸۰۳۵۲۵۰۴۱۰۰۲۵۱۱۳.

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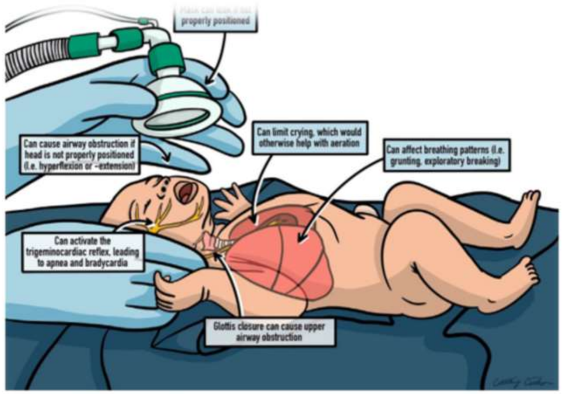
Bag and mask resuscitation is often not effective in the DR even when performed by the experienced personnel in extremely preterm infants.

four major issues with bag and mask ventilation are:

١-mask leak
٢-upper airway obstruction from the tongue falling backwards toward the oropharynx
٣-increase in dead space with the gas in the oropharynx not contributing to gas exchange
۴-trigeminocardiac reflex, a brainstem reflex that manifests as sudden cardiac perturbations including bradycardia, arterial hypotension, asystole, apnea, and gastric hypermobility



itfalls of Mask Ventilation.

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In newborn infants, respiratory depression or apnea during peripheral stimulation of any of the sensory branches of the trigeminal nerve have been described.

Reflex stimulation of the face, nose, or nasopharynx due to placement of face mask or insertion of nasal prongs can cause changes in respiration (decrease in breathing rates and an increase in tidal volume) and circulation (increase in cerebral blood flow) in newborn infants.

Gaertner VD, Rue¨gger CM, O'Currain E, et al. Physiological responses to facemask application in newborns immediately after birth. Arch Dis Child Fetal Neonatal Ed ۲۰۲۰;۱۰۶(۴):۳۸۱–۵.

However, there are limited data and further research is needed.

B.Barekatain

Successful use of RAM NC for the resuscitation of very low birth weight infants and decreased the need for intubation even among the lower gestational age infants (mean GA ۲۷ weeks) has been reported.

Biniwale M, Wertheimer F. Decrease in delivery room intubation rates after use of nasal intermittent positive pressure ventilation in the delivery room for resuscitation of very low birth weight infants. Resuscitation. (۲۰۱۷) ۱۱۶:۳۳–۸. doi: ۱۰.۱۰۱۶/j.resuscitation.۲۰۱۷.۰۵.۰۰۴.

B.Barekatain

For **noninvasive support**

Ram cannula is originally approved for delivering gases at low or high flows. However, because of the ease of use and lower nasal trauma, it is often used off-label for delivering n-CPAP, NIPPV, and n-HFOV.

Ram cannula looks similar to a traditional nasal cannula, but its stiffer design and higher diameter allows for delivery of higher flow and pressure. However, the pressures delivered by Ram cannula were found to be less than the Hudson prong and nasal masks.

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. ۲۰۲۰;۵۵:۱۶۳۱–۹.

There is no data to support use of Ram cannula in smallest of the babies and it has to be used with caution in extremely low-birth-weight (ELBW) neonates.

B.Barekatain

What is the best position for a baby under non-invasive respiratory support?(supine or prone)

The position of premature infants under N-CPAP is an important factor in their ventilation and oxygenation.

They can be placed in prone and supine positions.

Since it is easier to monitor babies in the supine position, the majority of premature infants are placed in this position.

However, the results of studies have shown that oxygenation is more improved in the prone position. the prone position also improves neural development, breathing control, and apnea and reduce heart rate changes and gastric reflux

To our knowledge, although the majority of studies have found the prone position to be better for oxygenation, some study conducted on infants with chronic lung diseases reported no difference between these two positions and reported a higher percentage of oxygen saturation in infants with supine positions.

B.Barekatain

What is the best method of weaning from non-invasive respiratory support?

١.Sudden weaning of NCPAP CICADA
٢.Gradual weaning of NCPAP pressure
٣.Graded-time-off NCPAP NCPAP cycling
۴.Weaning to high flow nasal cannula
۵.Weaning to low flow nasal cannula
۶.Combinations of the above methods

CICADA CeasIng Cpap At standarD criteriA

Stability criteria (must have all 8 criteria for ≥12 hours):-

1. CPAP 4-6 cm H_2O
2. Oxygen requirement less than 25% and not increasing
3. Respiratory rate less than 60
4. No significant chest recession (sternal/diaphragmatic)
5. Less than 3 episodes of self reverting apnoeas (<20 seconds) and/or bradycardias (<100 BPM) and/or desaturations (≤ 86%) in 1 hour for the previous 6 hours
6. Average saturation > 86% most of the time or PaO_2/transcutaneous PaO_2>45 mm Hg
7. Not currently treated for patent ductus arteriosus or sepsis
8. Tolerated time off CPAP during cares (up to 15 minutes)

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Which method is better?

A multicenter randomized controlled trial (RCT) was conducted in Australia on preterm infants <۳۰ weeks GA who were randomized into one of the three methods of ceasing CPAP

۱: CICADA
۲: cycling off gradually
۳: cycling off gradually with low flow cannula (LFNC) oxygen/air during time off NCPAP

They have shown that the CICADA method was superior to the other ۲ methods as it significantly reduced duration of NCPAP therapy, duration of oxygen therapy, CLD and the length of hospital stay.

Todd DA, Wright A, Broom M, Chauhan M, Meskell S,Cameron C, et al. Methods of weaning preterm babies <۳۰ weeks gestation off CPAP: a multicentre randomised controlled trial. Arch Dis Child Fetal Neonatal Ed ۲۰۱۲;۹۷:F۲۳۶-F۲۴۰).

B.Barekatain

Moreover, the CICADA method reduced the time to reach full feeds and stop caffeine.These authors later reported that the introduction of CICADA for ceasing CPAP in their NICU has significantly reduced time on CPAP in preterm infants <۳۰ weeks GA and may have benefits including earlier breastfeeding and lower hospitalization costs

Heath Jeffery R, Todd D, Broom M, Shadbolt B. CeasIng Cpap At standarD criteriA (CICADA): does implementation of CICADA make a difference? Arch Dis Child Fetal Neonatal Ed ۲۰۱۴;۹۹ Suppl ۱:A۵۹-A۶۱.

These data were confirmed subsequently in a large multicenter RCT which concluded that sudden weaning off NCPAP reduced the length of weaning time, duration of NCPAP, hospital stay, the incidence of BPD and the time to reach full feeds and stop caffeine therapy

Broom M, Ying L, Wright A, Stewart A, Abdel-Latif ME, Shadbolt B, et al. CeasIng Cpap At standarD criteriA (CICADA): impact on weight gain, time to full feeds and caffeine use. Arch Dis Child Fetal Neonatal Ed ۲۰۱۴;۹۹:F۴۲۳-F۴۲۵.

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Studies comparing different methods of weaning from NCPAP

Study	Study design	Sample size	Population	Comparison	Main results
Soe[41]	Single center RCT	98	24-31 wk gestation	Pressure weaning versus cycling	No difference between both methods in preterm infants ≥28 wk Pressure weaning is more appropriate in preterm infants <28 wk
Singh et al[32]	Multicenter RCT	112	<1500 g	Pressure reduction versus cycling to LFNC	The gradual reduction in NCPAP pressure may facilitate more rapid respiratory weaning compared with cycling to LFNC
Abdel-Hady et al[28]	Single center RCT	60	Preterm infants ≥28 wk gestation	Sudden weaning versus weaning to HHHFNC	No difference in weaning success Weaning preterm infants from NCPAP to HHHFNC is associated with increased exposure to oxygen and longer duration of respiratory support
Todd et al[37]	Multicenter RCT	154	<30 wk gestation	Sudden weaning versus cycling versus cycling to LFNC	Sudden weaning off CPAP was associated with significantly reduced length of weaning, duration of oxygen therapy, chronic lung disease and length of hospital stay
Rastogi et al[42]	Single center RCT	56	≤32 wk gestation	Sudden weaning versus cycling	No difference in success of weaning from NCPAP No difference in infants' weight and postmenstrual age at the time of successful weaning off NCPAP
O'Donnell et al[30]	Two-center RCT	78	<1500 g	LFNC air versus spontaneous breathing	No benefit in weaning VLBW infants from NCPAP to LFNC. However, the CIs were wide enough to accommodate substantial differences in success of weaning from NCPAP No significant differences in length of time to failure and change in heart rate, respiratory rate, oxygen saturation, and respiratory distress score
Fernandez-Alvarez et al[31]	Matched pair cohort study	79	≤28 wk and <1250 g	Weaning to HHHFNC versus LFNC	HHHFNC shortens NCPAP time without increasing overall length of non-invasive respiratory support in very preterm infants Unlike NCPAP, HHHFNC does not seem to increase the risk of nasal trauma and appears to improve cost effectiveness whilst producing otherwise equal respiratory and non-respiratory outcomes

NCPAP: nasal continuous positive airway pressure; HHHFNC: heated, humidified, high-flow nasal cannula; LFNC: low flow nasal canuula; RCT: randomized controlled trial; CIs: confidence intervals; VLBW: very low-birth-weight.

B.Barekatain

challenge

There is no consensus on defining the optimal timing for weaning. Moreover, the methods of weaning from the NCPAP have been variable and inconsistent across NICUs.

The role of other methods of non-invasive respiratory support such as HHHFNC and LFNC is still under investigation. Development of evidence-based guidelines based on clinical characteristics of the infants may help neonatologists to determine the best timing and method for weaning from NCPAP.

B.Barekatain

... And finally

What should be done in the future is that:

"different methods should be studied in clinical trials that can answer all the challenges and questions"

Dr B Barekatain