

Positive Pressure Ventilation in Preterm Infants in the Delivery Room: A Review of Current Practices, Challenges, and Emerging Technologies

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Keywords

Infants · Newborn · Newborn resuscitation · Delivery room

Abstract

Background: A major proportion of preterm neonates require positive pressure ventilation (PPV) immediately after delivery. PPV may be administered through a face mask (FM) or nasal prongs. Current literature indicates that either of these are associated with similar outcomes. **Summary:** Nonetheless, FM remains the most utilized and the best choice. However, most available FM sizes are too large for extremely preterm infants, which leads to mask leak and ineffective PPV. Challenges to providing effective PPV include poor respiratory drive, compliant chest wall, weak thoracic muscle, delayed liquid clearance, and surfactant deficiency in preterm infants. Mask leak, airway obstruction, poor technique, and inappropriate size are correctable causes of ineffective PPV. Visual assessment of chest rise is often used to assess the efficacy of PPV. However, its accuracy is debatable. Though end tidal CO₂ may adjudicate the effectiveness of PPV, clinical studies are limited. The compliance of a preterm lung is highly dynamic. The inflating

pressure set on T-piece is constant throughout the resuscitation, but the lung volume and dynamics changes with every breath. This leads to huge fluctuations of tidal volume delivery and can trigger inflammatory cascade in preterm infants leading to brain and lung injury. Respiratory function monitoring in the delivery room has potential for guiding and optimizing delivery room resuscitation. This is, however, limited by high costs, complex information that is difficult to interpret during resuscitation, and absence of clinical trials. **Key Messages:** This review summarizes the existing literature on PPV in preterm infants, the various aspects related to it such as the pathophysiology, interfaces, devices utilized to deliver it, appropriate technique, emerging technologies, and future directions.

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Introduction

Most neonates born at term gestation transition from fetal to neonatal life without any significant assistance. However, around 10% of newborns may require respiratory support immediately after birth [1]. The International Liaison Committee on Resuscitation (ILCOR)

and several national resuscitation councils identify effective positive pressure ventilation (PPV) to be the cornerstone of neonatal resuscitation [2–4]. PPV improves the functional residual capacity, delivers tidal volume (V_T), initiates spontaneous breathing, and facilitates gas exchange with the goal of minimizing lung and brain injury [5]. During face mask (FM) PPV, a relatively fixed peak inflation pressure (PIP) is used with the assumption that this will deliver an adequate V_T . However, the delivered V_T is rarely measured [2–4]. Instead, indirect clinical signs such as chest rise and improvement in heart rate are used to gauge the effectiveness of PPV [2–4]. As the lung gets aerated, the lung compliance changes. Hence, relying on a fixed PIP delivered through a T-piece resuscitator might result in over or under ventilation of the lung, thereby contributing to lung and brain injury [6]. In contrast to term neonates, up to 77% of preterm neonates require PPV immediately after birth during delivery room (DR) stabilization. Inappropriate resuscitation puts them at the risk of major morbidities such as bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH). Even PPV delivered through non-invasive interfaces can trigger inflammatory cascades that could injure the lung, brain, and other developing organs [7–9]. In this article, we review the current evidence on PPV in preterm infants, the pathophysiology behind it, currently utilized interfaces and devices used to deliver PPV, emerging technologies, and future directions.

Devices

A T-piece resuscitator, self-inflating bag (SIB), or flow-inflating bag (FIB) can be used to provide PPV in the DR. Simulation studies have reported that a T-piece resuscitator delivers a relatively consistent PIP and positive end expiratory pressure (PEEP) while an SIB is shown to be associated with inconsistent PIP delivery and does not have the provision to provide PEEP effectively [10]. Though PIP and PEEP delivered by an FIB may be highly variable, this inference was derived from studies, which were conducted with health personnel who were unfamiliar with the use of FIB [10]. In a cohort study, Guinsburg et al. [11] compared a T-piece resuscitator ($n = 1,456$) with an SIB ($n = 506$) and found that the T-piece resuscitator group had a higher likelihood of survival until hospital discharge (69% vs. 56%, $p < 0.001$), survival until hospital discharge without BPD (53% vs. 39%, $p < 0.001$), survival without BPD. The adverse outcomes of severe IVH (>grade 2) or periventricular leukomalacia were

found to be decreased in the T-piece group when compared to the SIB group (47% vs. 35%, $p < 0.001$). Furthermore, a recent meta-analysis of four trials ($n = 1,247$) reported that respiratory support with a T-piece resuscitator decreases the risk of BPD (risk ratio 0.64; 95% confidence interval [CI] 0.43–0.95) when compared to SIB. In-house mortality was comparable between the two groups [12]. These data suggest that a T-piece resuscitator may be more efficacious than SIB in neonates for providing PPV. Future studies may also consider evaluating FIB provided the healthcare personnel involved in these studies are appropriately trained in using FIB.

Interfaces

PPV can be delivered through an FM or short binasal prongs (SBPs) or nasopharyngeal tube (NPT). Concerns with FM use include incorrect sizing and triggering of the trigeminocardiac reflex (TCR) [13, 14]. A recent meta-analysis (5 trials, $n = 873$) reported no difference in in-hospital mortality (risk ratio [95% CI] 0.98 [0.63–1.52], $p = 0.92$) or morbidities when neonates are provided PPV with an SBP/NPT or an FM [15]. However, the meta-analysis excluded the largest randomized controlled trial (RCT) by Donaldsson et al. [16], which randomized neonates of >28 weeks' gestation to SBP ($n = 124$) or FM ($n = 122$). Donaldsson et al. [16] reported a decreased risk of DR intubations and mortality in the SBP group when compared to the FM group (33% vs. 45%, adjusted odds ratio [95% CI] 0.53 [0.30–0.94]; $p = 0.03$). There were no differences between the two groups for any of the secondary outcomes (use of surfactant, air leak syndromes, any IVH).

An alternative for either SBP, NPT, or FM is supra-glottic airway device (SAD), which has been shown to be effective in providing PPV in late-preterm and term infants. However, as of present a small-sized SAD that could be used in extremely low gestational age neonates is not available [17]. Smallest neonates where SAD was inserted in the studies on surfactant administration were those whose birth weight was between 1,000 and 1,250 g [17]. SADs, specifically laryngeal mask airways, have evolved over the past three decades. The advantages of laryngeal mask airways when compared to an FM include a decreased propensity to stimulate TCA reflex and a lesser risk of inadvertent placement in the esophagus or the right bronchus when compared to an endotracheal tube. Kamlin et al. [18] evaluated oropharyngeal airway for providing PPV in preterm neonates >34 weeks' gestation. The authors concluded that use of an oropharyngeal airway as an adjunct to FM PPV

significantly increased the risk of airway obstruction. This emphasizes the fact that the most important aspect of delivering effective PPV is the familiarity with the available equipment supplemented by frequent training in its usage.

Hand Positions during Mask Ventilation

There are currently no evidence-based recommendations on how to hold an FM during PPV. However, the European Resuscitation Guidelines recommend the two-person mask hold technique if PPV is ineffective [4]. Simulation studies have examined the two-point top hold [19, 20], stem hold [19], rim hold [19], spider hold [20], and the two-person mask hold techniques [20, 21]. Wood et al. [19] reported that the Laerdal round mask (Laerdal Medical, Stavanger, Norway) had a median (IQR) FM leak rate of 15% (0–18) with two-point top hold, 42% (17–62) with stem hold, and 23% (3–50) with rim hold. Meanwhile, the Fisher & Paykel round mask (Fisher & Paykel Healthcare, Auckland, New Zealand) leak rates were 40% (15–63) with two-point top hold, 50% (38–70) with stem hold, and 2% (1–10) with rim hold [19]. This study suggests that the leak around a particular type of FM is predominantly influenced by the holding technique. Additional studies have also showed high variability in FM leak rate with the aforementioned FM types and holds, suggesting that leak rate is heavily influenced by the provider as well. Wilson et al. randomized 53 participants to perform PPV with a Laerdal round mask using three different FM holds and reported no differences in FM leak rates (median [IQR]): two-point top hold 19% (2–38), spider hold 10% (3–49), two-person mask hold 9% (2–51)) [20]. A study with 48 participants (21,578 inflations) demonstrated that a single-person FM hold results in greater FM air leak compared to a two-person hold, whether an SIB (MD [95% CI] 6.1% [1.5–10.7], $p < 0.01$) or a T-piece resuscitator is used (MD [95% CI] 13.1% [3.6–22.6], $p < 0.01$) [21]. Shah et al. [22] randomized 25 preterm neonates of >30 weeks' gestation to PPV with either one-person or two-person mask hold and reported the mean (SD) FM leak with one-person technique being 26% (19) and with two-person technique being 18% (9). These studies suggest that the use of two-person FM PPV at birth is not only feasible but also may reduce FM air leak rates, thereby providing relatively more efficacious PPV. However, the two-person technique does require additional manpower (Fig. 1, 2). Though there is a biological plausibility that FM leak and consequent ineffective PPV may be associated with inadequate V_T delivery resulting in

poorer clinical outcomes, however, there is a lack of data to associate FM leak with adverse clinical outcomes. van Vonderen et al. [23] compared FM with nasal tube during PPV in preterm neonates of >30 weeks' gestation that reported a significantly high leak with nasal tube compared to FM {[98% (33–100%) vs. 14 (0–39%); $p < 0.0001$]}. On the contrary, Kamlin et al. [24] randomized preterm neonates born at >30 weeks' gestation to FM versus nasal tube and did not report any differences in the critical outcomes of death and/or BPD. There was also no difference in endotracheal intubation, severe grade IVH, and necrotizing enterocolitis. The major limitation of this study was that the leak around the FM or nasal tube was not assessed precluding any reasonable conclusions.

FM Leak

Mannequin studies have reported variable FM leak rates, which occur irrespective of the level of training [25, 26]. FM leak during PPV is often underrecognized and can result in ineffective ventilation [6, 27, 28]. A major reason for FM leak is the unavailability of FMs of appropriate size. O'Shea et al. [29] photographed faces of preterm infants of gestational age 24–33 weeks and reported that the smallest available size of FM is too large for many of the preterm infants. However, two RCTs compared smaller and larger FMs during PPV in the DR and reported no difference in FM leak (between 30 and 42% for both the types of FMs) [30, 31].

FM leaks may be recognized and corrected timely using a feedback device such as a respiratory function monitor (RFM) [32–35]. Furthermore, RFM when used as adjunct to traditional training has been shown to improve the efficacy of FM PPV. Of the three studies conducted till date on RFM, two had reported a reduction in the FM leak with RFM. Though these are encouraging findings, there is a concern that additional information provided by an RFM may not be adequately interpreted by the healthcare professional [36, 37]. More recently, newer RFMs featuring more user-friendly features and improved efficiency in detecting FM leak have been introduced. Further studies evaluating their performance are warranted.

Airway Obstruction and Glottis Closure

Airway obstruction might occur during PPV due to excessive force applied during FM ventilation, incorrect positioning of the head in relation to the neck,

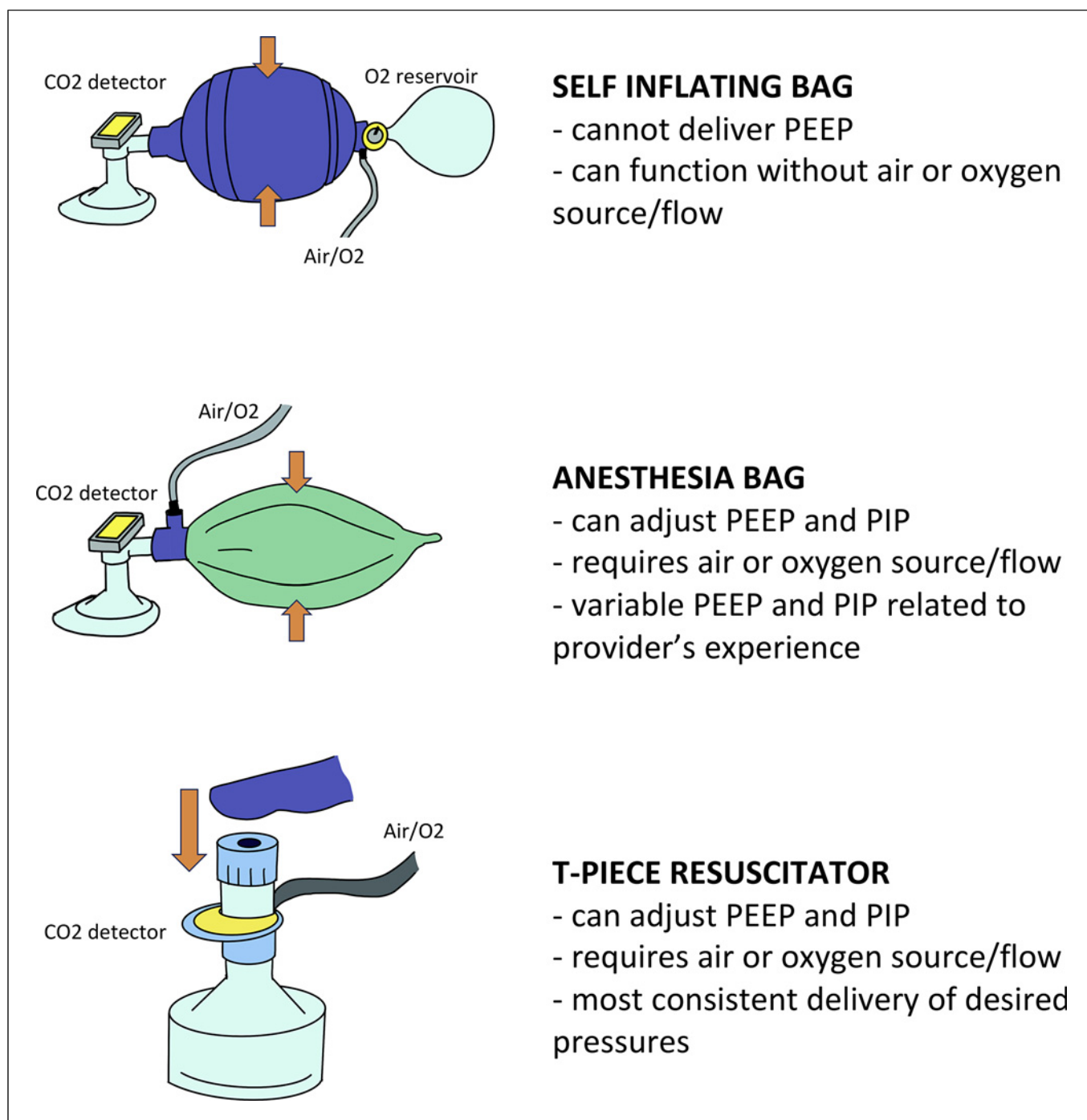


Fig. 1. Type of available devices to deliver PPV: SIB (top), FIB (middle), T-piece (bottom).

inappropriate mask size, or secretions obstructing the airway [27, 38]. Studies from the last decade had indicated that airway obstruction during FM PPV occurs in up to 75% of cases (based on exhaled CO₂ [ECO₂] or RFM waveforms) [27, 38]. These findings have led to

studies suggesting that ECO₂ detectors or RFMs may help identify airway obstruction [39]. While an RFM can display obstructed waveforms, more recent studies have highlighted that airway obstruction might be due to glottis closure. Glottis closure is a fetal mechanism,

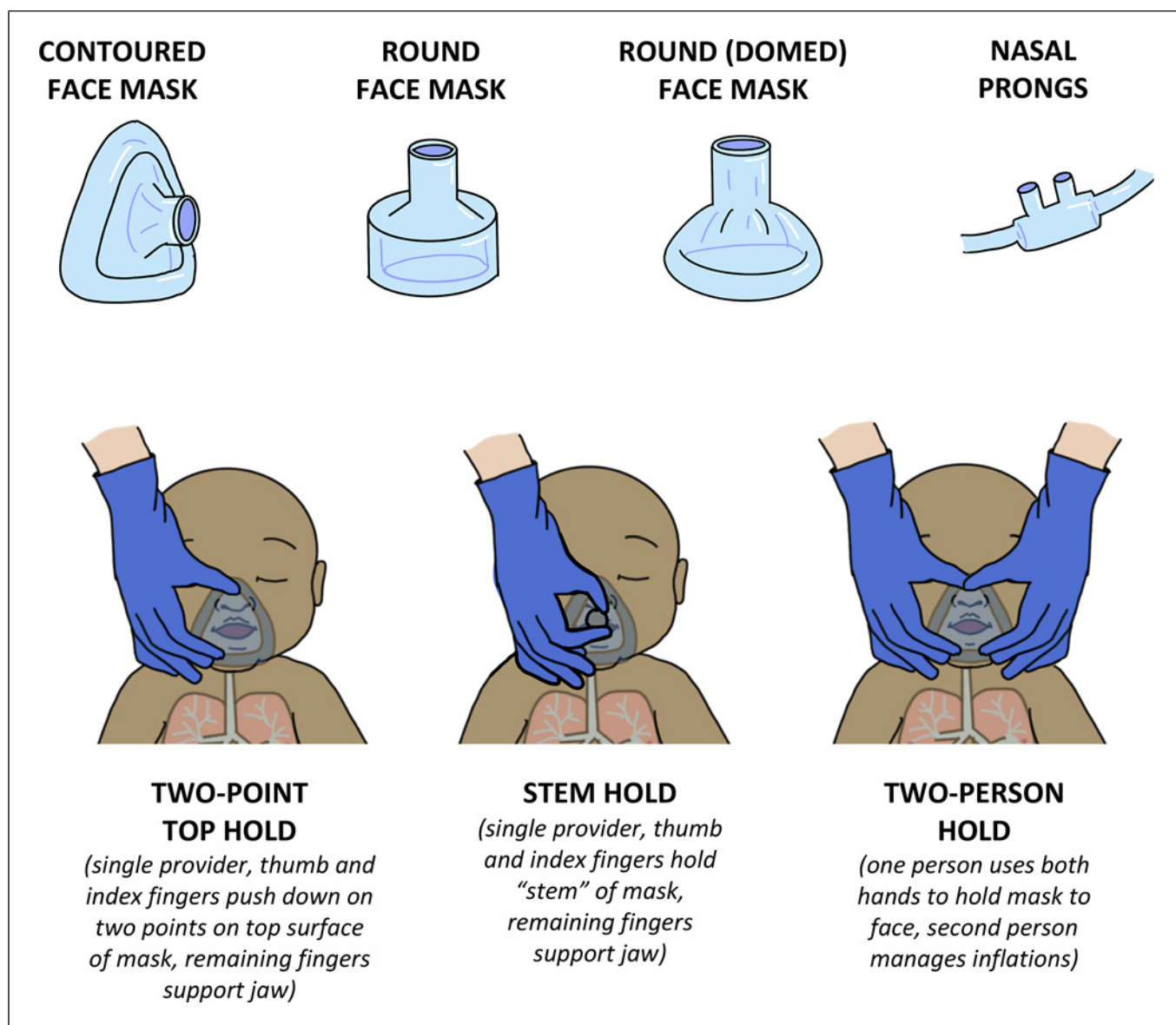


Fig. 2. Various interfaces available to deliver PPV (top row) and holding techniques (bottom row).

which allows for adequate maintenance of fluid and pressure within the developing fetal lung thereby keeping them distended and allowing for the adequate fetal lung growth and development. During stabilization after birth, a closed glottis impedes the delivery of respiratory support [40]. Craswshaw et al. [41] reported that in rabbit pups, the larynx and epiglottis were predominantly closed (open in only ~20%) with un-aerated lungs or unstable breathing patterns immediately after birth. However, when the lungs were aerated with stable breathing pattern, the larynx and the epiglottis

were mostly open (~90% of the time) [41]. van Vonderen et al. [40] reported that glottis closure affects the delivery of effective PPV and a sustained inflation for 10 s and 25 cm H₂O was ineffective unless infants initiated breathing. Rarely, in the setting of severe in-utero hypoxia, the fetal glottis may be functionally compromised and can remain open for a prolonged period of time resulting in aspiration of amniotic fluid containing fetal lung fluid, urine, skin debris, and other particulate matter such as meconium resulting in various types of aspiration syndrome.

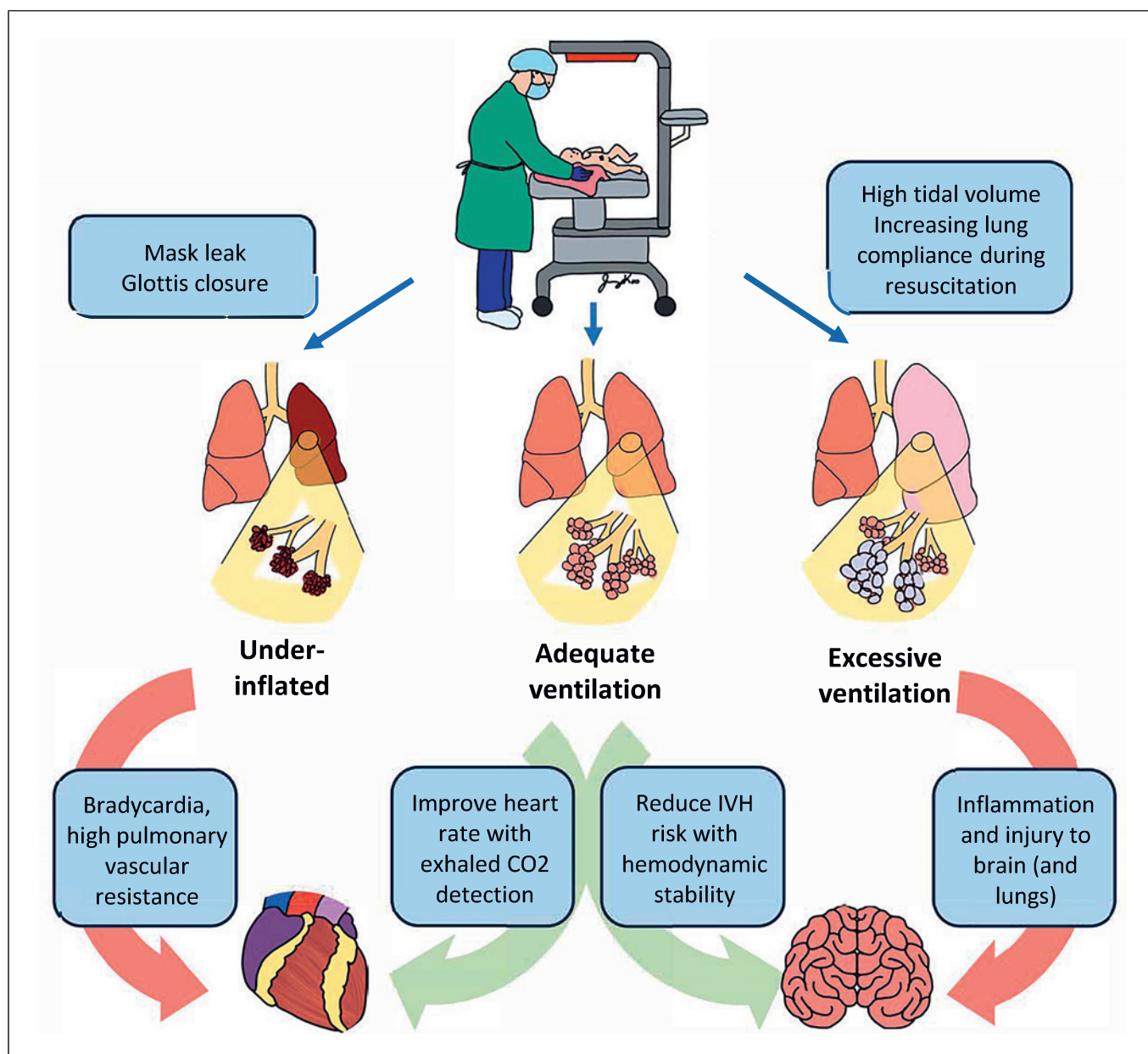


Fig. 3. PPV and its effects.

Trigemino-cardiac Reflex

TCR, also known as the diving reflex, can be triggered by stimulating either of the three branches of trigeminal nerve. The TCR is triggered by exposure to cold air, water, or pressure over maxilla or mandible and is inherently designed by the body to prevent aspiration [42]. The TCR leads to the closure of the glottis to prevent aspiration, often followed by peripheral vasoconstriction, slowing of the heart

rate, and breathing to preserve oxygen consumption [42]. In preterm neonates, application of an FM may trigger the TCR [13, 14]. This may be accompanied by apnea, lower heart rate, lower oxygen saturations, as well as requirement of a higher rate of PPV [13, 14]. An alternative interface might be SBPs. However, a recent meta-analysis of available trials did not find any differences in clinical outcomes and none of the studies assessed the outcomes of apnea, heart rate, and oxygen saturation in the DR [15].

Peak Inflation Pressure and V_T

The ILCOR Neonatal Task Force and the American Heart Association guidelines on neonatal resuscitation recommend initiating PPV with a PIP of 20–25 cm H₂O in preterm infants [2–4]. However, this recommendation is not based on high evidence certainty. Animal studies have demonstrated that lung injury can occur with just a few large manual inflations of 35 mL/kg and that lung injury is mainly caused by volutrauma and not barotrauma [43, 44]. In the DR, the delivered V_T ranges from 0 to 30 mL/kg [6, 45], and excessive V_T delivery has been shown to be associated with adverse outcomes of BPD and IVH [8, 9, 46]. Since the neonatal lung is initially fluid filled, the V_T delivery will depend on the lung compliance, airway resistance, and PIP [47, 48]. As the lung aerates, lung compliance rapidly improves, which results in higher V_T delivery if a static PIP is used. While an RFM has been shown to reduce excessive V_T delivery, none of the studies published to date have demonstrated improvements in critical or important clinical outcomes [32–35]. An alternative might be a ventilator-delivered targeted V_T as practiced in the NICU. Simulation studies have reported that PPV using a set V_T on a ventilator reduced FM leaks and variations in V_T delivery [49–51]. Further studies are necessary before implementing these practices in the DR. The adverse effects associated with delivering inadequate V_T during neonatal resuscitation is depicted in Figure 3.

Inflation Times (Ti)

The European Resuscitation Guidelines recommend a Ti of up to 2–3 s for the first 5 inflations. However, the optimal Ti remains unknown [4]. In spontaneously breathing preterm neonates, the Ti varies between 0.35 and 0.40 s depending on the breathing pattern [52]. Klingenberg et al. [53] compared PPV with a Ti of 0.5 s, 5 breaths of 3 s inflations, and a single 30 s inflation in near-term asphyxiated lambs and reported that the median time to reach a HR of 120 beats/min was significantly shorter in the single 30 s inflation group when compared to the 5 breaths of 3 s inflations group and the conventional ventilation group (8 s, 38 s, and 64 s), respectively. However, there have been no study in preterm neonates or animal models evaluating the optimal Ti to be used during FM PPV. As the lung is initially liquid filled, the Ti required will be different when compared to an aerated lung to achieve similar V_T [47, 48, 54]. Though the exact pathophysiology behind clearance of lung fluid immediately after birth is not fully understood, pre-clinical studies demonstrated that lung fluid clearance

depends on many factors including gestational age, onset of labor (spontaneous vs. induced), and mode of delivery (vaginal vs. caesarean section). Hence, it is plausible that the Ti required to adequately expand the lung might vary based on these aspects and future studies may evaluate the different Ti required based on these factors. The Sustained Aeration of Infant Lung (SAIL) trial randomized preterm neonates of 23–26 weeks' gestation to sustained inflations or intermittent PPV [55]. The outcome of mortality within the first 48 h of life was significantly higher in the sustained inflation group when compared to the standard resuscitation group (7.4% vs. 1.4%, aRD [95% CI] 5.6% [2.1–9.1%], $p = 0.02$).

Positive End Expiratory Pressure

One of the most important aspects of DR stabilization is providing optimal PEEP. Providing appropriate PEEP aids in recruiting the alveoli and keeping the lungs open, especially those born extremely premature. It remains unclear what the optimal PEEP is to maintain an open lung. There are two types of PEEP delivery strategies either using a static PEEP or a dynamic PEEP approach [56, 57]. The static approach uses a PEEP of 5–8 cm H₂O while with the dynamic PEEP approach, the PEEP level is individualized and varies based on the clinical status of a preterm neonate. The concept of dynamic PEEP involves varying the PEEP level between 8 and 12 cm H₂O based on clinical response. A large multi-center trial is currently ongoing (the POLAR trial, NCT04372953), which will provide further insights into the dynamic PEEP approach.

Stimulation

One of the initial steps of neonatal resuscitation include stimulation; this could be done by rubbing of the back, chest, or soles at birth [2–4]. However, the intensity, location, and duration of stimulation are yet to be evaluated in RCTs. Studies in preterm neonates have reported that stimulation during the initial steps of resuscitation result in a significant increase in oxygen saturation but not the heart rate and may also influence spontaneous breathing [58–60]. Furthermore, Dekker et al. [61] randomized 44 preterm neonates to repetitive stimulation versus standard tactile stimulation and reported that SpO₂ values were significantly higher with repetitive stimulations when compared to standard stimulation practices (87.6 [3.3]% vs. 81.7 [8.7%], $p = 0.01$). Katheria et al. [62] randomized preterm neonates of 23–31 weeks' gestation to either delayed cord clamping (DCC) with assisted ventilation versus DCC alone. The time to spontaneous breathing was similar in both groups. Furthermore, the DCC alone group received stimulation for

almost double the time compared to the DCC plus assisted ventilation group. These results suggest that adequate stimulation during DCC in preterm infants should be provided. While these results are promising, further trials akin to the NEU-STIM trial (NCT05942924) ($n = 3,280$) may further strengthen the evidence certainty.

Changes in Heart Rate

The 7th edition of the Neonatal Resuscitation Program textbook states that “If PPV was started because the infant had a low HR, the infant’s heart rate should begin to increase within the first 15 seconds of PPV assuming that adequate ventilation is achieved” [63]. DR studies have reported that heart rate may not always increase within the first 15 s of PPV [64]. Heart rate increases through two different patterns: (1) gradual rise to more than 100 beats/min over 60 s or (2) a rapid increase within 5 s after lung aeration [64]. Espinoza et al. [65] further reported that in asphyxiated piglets receiving PPV, around 50% of piglets do not display an increase in HR within 30 s. Linde et al. [66] reported a non-linear relationship between delivered V_T and HR increase with a V_T of 9.3 mL/kg resulting in the highest likelihood of an increase in heart rate during PPV. Frequent interruptions of PPV to provide stimulation or suctioning occurred in all cases and was associated with further increase in heart rate, especially in newborns with an initial heart rate of >100 beats/min [66]. A rising heart rate remains the best indirect indicator that gas exchange has been achieved and thereby is one of the most reliable surrogate marker indicating adequate ventilation.

Respiratory Function Monitor Guidance

A RFM can be used for training the healthcare personnel in the DR to guide respiratory support by adding objectivity to the clinical assessment [67]. It may be used to teach correct FM hold and positioning techniques during simulation-based training [68]. O’Currrain et al. [68] randomized 400 healthcare providers to either have the RFM displayed (intervention group) or masked to RFM (control group) during a structured newborn resuscitation training course. Overall, providers who were randomized to have visuals on the RFM had significant lower mask leak (23% vs. 35% [$p < 0.0001$]) compared to providers without RFM guidance. While this study supports the use of an RFM during training, Fuerch et al. [69] in their recent ILCOR systematic review, which included three RCTs ($n = 443$), concluded that use of an RFM in the DR during PPV did not result in improved clinical outcomes of intubation rate, air leaks, mortality before hospital discharge, severe IVH, and BPD.

Exhaled CO_2

ECO_2 is an excellent tool to assess lung aeration after birth [70]. Animal and clinical studies have indicated a strong correlation between the detection of ECO_2 and the increase in HR during the time of resuscitation [70]. Studies conducted in term neonates have also reported that it takes only a few breaths (median [IQR] 7 [4–11] breaths) until the ECO_2 could be measured (median [IQR] 15 [12–20] mm Hg) [71]. In preterm neonates receiving PPV, the median time to achieve an ECO_2 of more than 10 mm Hg or a color change in the ECO_2 was reported to be 80–95 s. Further, there was a delay of 10–28 s from the time of ECO_2 detection and increase in HR (>100 beats/min) [72]. While the results from the aforementioned studies are promising, the ILCOR Neonatal Task Force has not recommended the use of ECO_2 during newborn resuscitation as the evidence base remains limited [73].

Conclusions

Providing effective PPV is the most important aspect in neonatal resuscitation, especially in preterm neonates. Delivering effective PPV mandates repeated training and practice for bettering clinical outcomes. The efficacy and safety of delivered PPV may have a major impact on optimizing resuscitation in preterm neonates when compared to term neonates. Henceforth, focusing on improving the delivery of PPV by reducing the leak around the FM, using a T-piece resuscitator with appropriately sized FM or SBP, proper technique and with knowledge on trouble-shoot issues such as glottic closure, airway obstruction, and TCR is of utmost importance. Though the use of ECO_2 or RFM in the DR has been shown to be useful as an adjunct, whether their use translates to better clinical outcomes needs further studies.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design: G.M.S. Collection and assembly of data, analysis and interpretation of the data, critical revision of the article for important intellectual content, and final approval of the article: G.M.S., S.D., V.V.R., J.K., and A.P. 1st draft of the article: G.M.S. and S.D.

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