Nasal Continuous Positive Airway Pressure (CPAP) for the Respiratory Care of the Newborn Infant

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Nasal continuous positive airway pressure (CPAP) is a noninvasive form of respiratory assistance that has been used to support spontaneously breathing infants with lung disease for nearly 40 years. Following reports that mechanical ventilation contributes to pulmonary growth arrest and the development of chronic lung disease, there is a renewed interest in using CPAP as the prevailing method for supporting newborn infants. Animal and human research has shown that CPAP is less injurious to the lungs than is mechanical ventilation. The major concepts that embrace lung protection during CPAP are the application of spontaneous breathing at a constant distending pressure and avoidance of intubation and positive-pressure inflations. A major topic for current research focuses on whether premature infants should be supported initially with CPAP following delivery, or after the infant has been extubated following prophylactic surfactant administration. Clinical trials have shown that CPAP reduces the need for intubation/mechanical ventilation and surfactant administration, but it is still unclear whether CPAP reduces chronic lung disease and mortality, compared to modern lung-protective ventilation techniques. Despite the successes, little is known about how best to manage patients using CPAP. It is also unclear whether different strategies or devices used to maintain CPAP play a role in improving outcomes in infants. Nasal CPAP technology has evolved over the last 10 years, and bench and clinical research has evaluated differences in physiologic effects related to these new devices. Ultimately, clinicians' abilities to perceive changes in the pathophysiologic conditions of infants receiving CPAP and the quality of airway care provided are likely to be the most influential factors in determining patient outcomes. *Key words: continuous positive airway pressure, CPAP, nasal CPAP, infant mechanical ventilation, neonatal intensive care*. [Respir Care 2009;54(9):1209–1235.

Introduction

Nasal continuous positive airway pressure (CPAP) is a noninvasive method for applying a constant distending pressure level (above atmospheric) during inhalation and exhalation to support spontaneously breathing newborn infants with lung disease. CPAP is an "open-lung approach" used to manage newborn infants predisposed to developing airway instability, edema, and atelectasis. The clinical goals of CPAP are to maintain the functional residual capacity (FRC) of the lungs and support gas exchange to reduce apnea, work of breathing (WOB), and lung injury. CPAP is most commonly delivered to the nasal airway opening using bi-nasal short prongs or a nasal mask, and pressure is generated using a variety of devices. CPAP is generally well tolerated, and usually effective, in part because infants are preferential or "obligatory nasal-breathers,"[1,2] and pressure is maintained in the lungs due to the anatomic seal that forms between the infant's tongue and the soft palate.[3]

CPAP is most frequently applied in premature infants with respiratory distress syndrome (RDS). However, CPAP has also been used to treat infants with other respiratory disorders, including transient tachypnea of the newborn,[4] meconium aspiration syndrome,[5,6] primary pulmonary hypertension,[6] pulmonary hemorrhage,[7] patent ductus arteriosus[8] and consequent pulmonary edema.[9] CPAP improves lung function following surgical repair of congenital cardiac anomalies,[10-12] paralysis of a hemidiaphragm, and is an effective option for infants following surgical repair of diaphragmatic hernia.[13] CPAP is also effective in managing infants with respiratory infections, such as congenital pneumonia[14] or respiratory syncytial virus bronchiolitis.[15,16] CPAP is useful for treating obstructive and central apnea of prematurity and congenital and acquired airway lesions. CPAP is contraindicated in patients with upper-airway abnormalities (ie, cleft palate, choanal atresia, tracheoesophageal fistula), unrepaired diaphragmatic hernia, severe cardiovascular instability, recurrent apneic episodes, and in patients with severe ventilatory impairment (pH < 7.25, and $P_{aCO_2} > 60$ mm Hg).[17]

Resurgence in the popularity of CPAP has become increasingly evident over the last decade. It is less expensive, easier to operate, poses potentially fewer risks, and requires less training than does intubation and subsequent conventional mechanical ventilation. Despite its advantages, questions remain about how best to manage infants on CPAP. Little is known of the appropriate initial CPAP level and whether this setting should change depending on the disease process, birth weight, and with changes in the pathophysiologic condition of the patient. Limits for acceptable blood gas levels and methods for determining lung recruitment in infants receiving CPAP are undefined. At present, the most pressing issue is whether CPAP should be applied in premature infants immediately after birth or following brief intubation for surfactant administration.

The fundamental role of the bedside clinician in the care of infants supported by CPAP is evolving. Patients receiving CPAP may often require the same level of attention, or more than those supported with mechanical ventilation. The apparent success of CPAP may be more related to the meticulous airway management and the high level of bedside involvement. A proliferation of new CPAP technologies and management strategies have come a long way in an extremely short period of time, and, thus, one is left to speculate whether these factors ultimately play a role in patient outcomes. The specific aims of this review paper are to provide clinicians with a comprehensive updated summary of the literature to better determine the clinical responses in infants supported by CPAP, describe the operational principles and physiologic effects related to CPAP systems, and define the role of CPAP for improving outcomes in premature infants with RDS.

History

In 1914, Von Reuss recognized Von-Tiegel's "overpressure apparatus," in the classic German text, *The Diseases of the Newborn*.[18] In this report, spontaneously breathing newborn infants were successfully managed using a simple system consisting of hoses, an oxygen gas source, a tight-fitting face mask, and a water-filled receptacle. A metal tube attached to the expiratory hose allowed gas to exhaust below the water surface, and pressure was varied by adjusting the tube depth according to a centimeter scale on the receptacle.[19,20]

In the later part of the 1960s and early 1970s, ventilators designed for use in adults were applied experimentally, and often unsuccessfully, to treat infants with severe respiratory failure.[21] In 1971, Gregory et al were the first to report the successful application of CPAP in a series of spontaneously breathing premature infants with RDS.[22] The initial goal of this novel form of support was to at-

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tempt a new strategy to reduce the already high mortality rates (60%) and chronic morbidities common to premature infants receiving mechanical ventilation during this era.[23] "Following the introduction of CPAP, the mortality of RDS decreased from 55–35% to 20–15%, an improvement which is comparable with the effect obtained by the introduction of surfactant 20 years later."[24] These developments led to the more widespread and routine use of CPAP, as well as investigations into improving the application of CPAP in infants.

The majority of CPAP, during this era, was administered using an endotracheal tube (ETT). The increasing awareness of ETTs' ability to impose a relatively high level of impedance during spontaneous breathing and affect airway injury and colonization led to new developments for applying CPAP to infants. Bancalari et al designed an experimental apparatus that provided a continuous distending pressure across the lung by applying negative pressure (4–10 cm H_2O) to the chest wall of a spontaneously breathing infant placed within a hermetically sealed plastic box.[25,26] Kattwinkel et al[2] and Caliumi-Pellegrini et al[27] described the initial experience using short bi-nasal prongs to deliver CPAP. In a small case series of infants supported using nasal prongs and a T-piece CPAP system, similar to that reported by Gregory et al,[22] 82% never required any other form of support, including mechanical ventilation.[2]

Ventilators specifically designed for use in infants were introduced in the late 1970s, which replaced CPAP as an initial strategy in most centers, and, thus, time-cycled pressure-limited ventilators became the preferred method of neonatal respiratory support for nearly 40 years. The more recent understanding of the role of ventilator-induced lung-injury in the pathogenesis of chronic lung disease (CLD) in premature infants has encouraged clinicians to favor, once again, "gentler," less invasive respiratory management strategies.

Physiologic Effects

Various physiologic effects have been evaluated to better determine the role of CPAP in supporting infants with lung disease. However, these physiologic effects are likely to vary, depending on the severity of lung pathology and whether lung disease is characterized by a restrictive or obstructive pattern. Inherent differences in the operation of widely used CPAP systems may also impact the lung pathophysiology differently, and experimental data reviewing these details will be presented later in this discussion.

CPAP is a form of positive pressure; however, the major fundamental difference between CPAP and mechanical ventilation is that CPAP is unable to effectively sustain alveolar ventilation during apnea, and, therefore, patients must be able to generate all of the breathing efforts. Through the application of pleural pressure changes, spontaneous breathing at a sustained distending pressure augments venous return, improves cardiac output, and promotes better aeration in dependent lung units, favoring alveolar recruitment and stabilization.[28-30]

CPAP mimics the natural physiologic reflex, "grunting," that is frequently exhibited in infants with low lung compliance and low end-expiratory lung volume.[10] Grunting is the dynamic expiratory braking phenomenon, resulting from vocal cord adduction and diaphragmatic contraction, which limits airflow during exhalation and maintains transpulmonary pressure and end-expiratory lung volume above the critical closing pressure of the lungs.[10,31,32] Early attempts to try to replicate effects associated with grunting was the premise by which Gregory et al originally sought to develop the first widely used CPAP systems.[10] The compensatory volume-preserving expiratory braking maneuver associated with grunting is abolished by CPAP, which suggests that CPAP can sufficiently produce a similar effect.[33] Infants with lung disease also develop tachypnea to reduce expiratory time and, thus, limit exhalation of gases to preserve end-expiratory lung volume. CPAP reduces tachypnea and increases FRC and P_{aO_2},[34] decreases intrapulmonary shunting,[35] improves lung compliance,[10] and aids in the stabilization of the floppy infant chest wall.[36]

The reduction in respiratory frequency is not so much related to ventilatory response to CO_2 during CPAP[37] as to the initiation of stretch receptors (Hering-Breuer reflex),[38] reductions in alveolar dead space,[10] improvements in the ventilation-perfusion ratio,[26,33,39,40] increases in distribution of ventilation,[34] and increased expiratory time and end-expiratory lung volume.[33] Although CPAP does not significantly augment alveolar minute ventilation per se, respiratory-syncytial-virus-infected infants supported with CPAP exhibit better ventilation (P_{aCO_2}) than do infants receiving only supplemental oxygen ($P < .02$).[41] This improvement in P_{aCO_2} may thus be explained by the role of CPAP in reducing pulmonary airway resistance.[38]

Reductions in levels of the inspiratory WOB are readily apparent, as indicated by decreases in nasal flaring, grunting, retractions, and tachypnea following the initiation of CPAP. Lipsten and colleagues demonstrated that the inspiratory WOB was lower in a series of premature infants using CPAP levels of 4–8 cm H_2O than in infants not using CPAP.[42] CPAP also decreases thoracoabdominal asynchrony[43] and labored breathing index.[44]

CPAP is an efficacious technique for supporting infants with congenital or acquired airway lesions that are prone to collapse (eg, tracheomalacia). In such cases, CPAP may improve airway function and relieve airway obstruction by increasing airway stiffness and diameter, which decreases the transmural collapsing pressure and minimizes premature airway closure.[45,46] CPAP may reduce additional air-

way complications by eliminating the need for tracheostomy and/or prolonged mechanical ventilation.[47]

Nasal CPAP can reduce the incidence and severity of central and obstructive apneic episodes in infants, through a number of physiologic mechanisms. CPAP is effective for obstructive apneas because it splints the upper airway open, thereby reducing the risk of pharyngeal or laryngeal obstruction.[48,49] By improving FRC and, hence, oxygenation, infants are also less likely to develop severe central apnea, with less incidence of deterioration in gas exchange. There has been some speculation that the physical contact and/or airflow stimulation of the nasopharynx provided by CPAP may further reduce the incidence of central apneas. Kurtz et al evaluated the effect of discontinuing CPAP and found that infants, supported by CPAP had significantly lower respiratory rates, fewer obstructive apneas, shorter central apneas, less severe apnea-associated desaturations, and spent more time in a state of normal quiet breathing than did infants breathing without CPAP.[50]

By avoiding endotracheal intubation and mechanical ventilation, the constant distending pressure maintained in the lung by CPAP may also provide some physiologic benefits regarding lung protection and development. In utero the transpulmonary pressure of the fluid-filled developing lung is approximately 3–4 cm H_2O.[51] Coincidently, CPAP at 5 cm H_2O results in nasal pharyngeal distending pressure of approximately 2–3 cm H_2O.[52] In theory, spontaneous breathing, at a constant "low" distending pressure, as provided by CPAP, would seem to be more likely to provide some mechanical similarities to the lungs in the intrauterine environment, promoting lung growth/development and protection, than would mechanical ventilation, which uses relatively high inflation pressure. Much of the experimental evidence used to evaluate these physiologic effects has been limited to a few studies using animal models of prematurity.

Jobe et al randomized premature lambs to receive mechanical ventilation to target P_{aCO_2} of 40 mm Hg or CPAP, with spontaneous breathing, at a level of 5 cm H_2O for 2 hours and compared indicators of lung injury between these 2 groups. At 2 hours, lungs of animals treated with CPAP held more gas volume at a static deflation pressure of 40 cm H_2O than did animals supported with mechanical ventilation (74 ± 4 mL/kg vs 60 ± 3 mL/kg, $P < .05$). In addition, the CPAP group had fewer neutrophils ($P < .05$) and cells containing lower hydrogen peroxide levels ($P < .05$) in alveolar washes than did the ventilated group.[53]

In a separate experiment, Jobe et al demonstrated that spontaneously breathing premature lambs, maintained on a CPAP level of 8 cm H_2O, had better oxygenation ($P < .05$) and lower minute ventilation ($P < .05$) at similar P_{aCO_2} levels than did animals maintained on a CPAP level of 5 cm H_2O for 6 hours. Animals supported with 8 cm H_2O also had better lung volumes at several static lung deflation maneuvers than did animals supported with mechanical ventilation ($P < .05$, Fig. 1). Animals supported with CPAP of 5 and 8 cm H_2O had higher wet-to-dry ratios than did animals supported with mechanical ventilation ($P < .05$).[54]

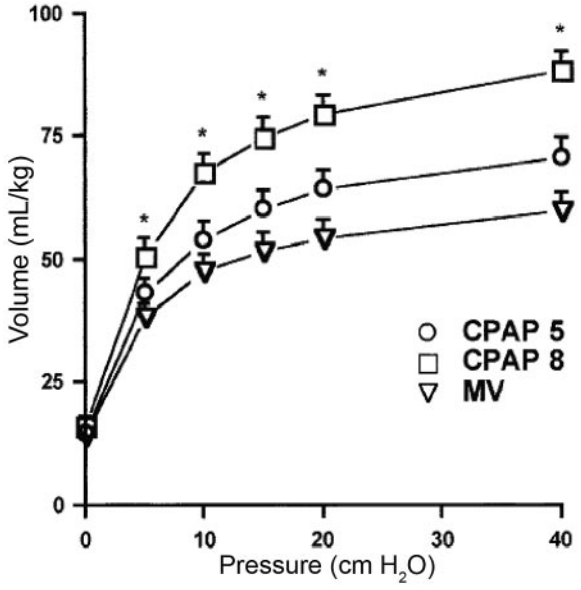

Fig. 1. Deflation pressure-volume curves for premature lambs on continuous positive airway pressure (CPAP) of 5 cm H_2O, CPAP of 8 cm H_2O, or mechanical ventilation (MV) for 6 hours. The lung gas volumes were larger in the lambs on CPAP of 8 cm H_2O than in those on mechanical ventilation (* $P < .05$ via 3-way analysis of variance). (From Reference 53, with permission.)

Data from these studies help to support the growing body of evidence that CPAP is less injurious than mechanical ventilation in premature infants. However, Polglase et al infected premature lambs intratracheally with *Escherichia coli* endotoxin and supported the animals with either CPAP or mechanical ventilation, and were unable to observe any physiologic benefits of CPAP over mechanical ventilation in reducing or limiting lung injury or systemic inflammatory responses.[55] These findings may have important clinical implications for infants exposed to antenatal infections (ie, chorioamnionitis), which can expose the premature lung to inflammation and injury following delivery.[56]

Thomson et al evaluated pathophysiologic differences using an established 28-day baboon model of prematurity/CLD[57] to compare differences in lung injury responses of animals supported with 2 different CPAP strategies.[58] The first group of animals was managed with brief ventilation (1 d) with extubation to early CPAP (early-CPAP group, $n = 6$) for 27 days. The second group was managed with a strategy using prolonged ventilation (5 d) and delayed extubation to CPAP (delayed-CPAP group, $n = 5$) for 23 days. All animals were treated similarly, using prenatal steroids, exogenous surfactant, lung-protective ventilation

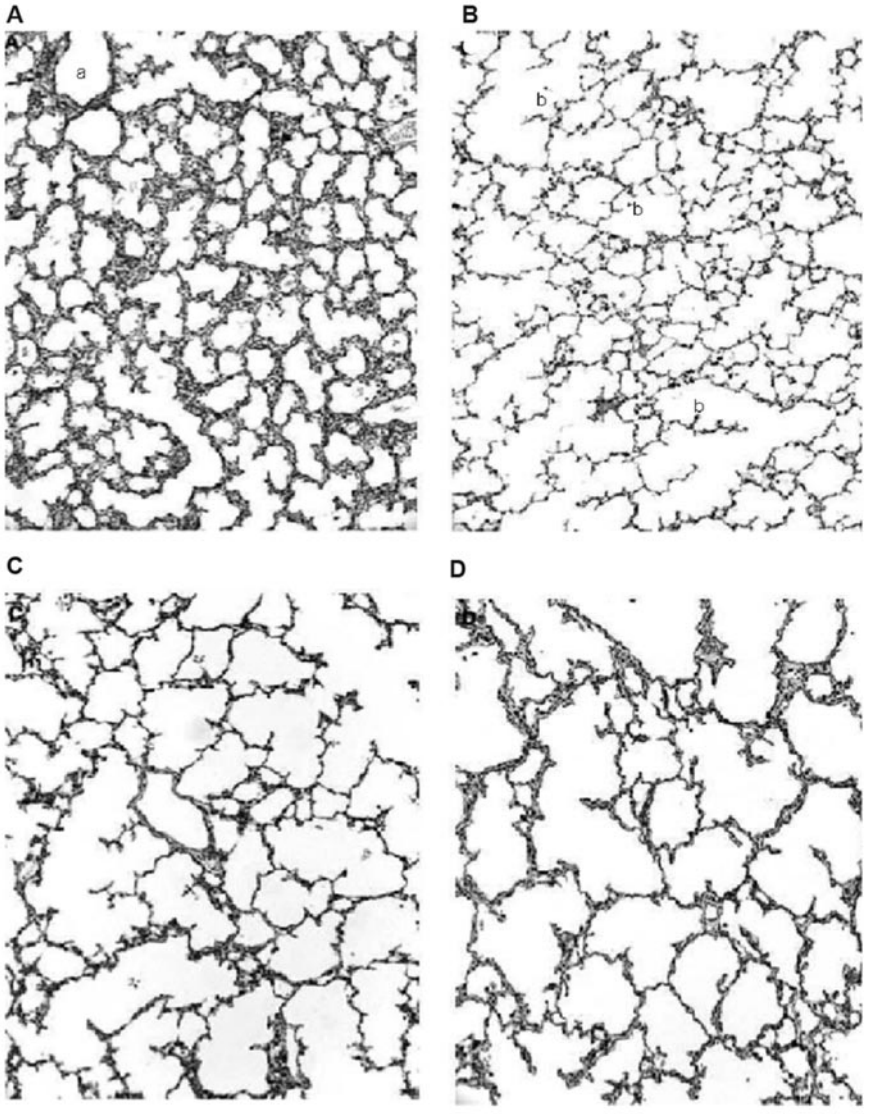

Fig. 2. A: 125-day gestational control. Bronchioles and rounded saccular spaces with thickened walls. Bulges or protuberances from walls into air spaces are progenitor secondary crests. B: 153-day gestational control. Air spaces larger than 125-day control, and thinned saccular walls have abundant secondary crests and alveolar structures. C: Early nasal continuous positive airway pressure (CPAP) 28-day specimen. Air spaces well expanded, and thinned saccular walls show increase in alveolar complexity (ie, elongated branching walls with secondary crests and alveolar formation). D: Delayed nasal CPAP 28-day specimen. Walls of thinned saccular structures may be slightly more cellular than early nasal CPAP, but ongoing alveolar formation is present. (Hematoxylin and eosin: original magnification 10.) (From Reference 58, with permission.)

(tidal volume of 4–6 mL/kg), and an initial CPAP level of 7 cm H_2O. Animals treated with delayed CPAP exhibited greater detrimental pathophysiologic effects than did animals treated with early CPAP. Animals treated with delayed CPAP exhibited poorer respiratory drives, with consequentially greater requirements for intubation and ventilation, more cellular bronchiolitis, alveolar wall thickening (Fig. 2), and significantly elevated pro-inflammatory cytokines/chemokine levels than did the early-CPAP group. These data suggest that volutrauma and/or low-grade bacterial colonization secondary to increased re-intubations and prolonged ventilation may play causative roles in promoting lung injury and limiting lung growth and development in premature infants.

Nasal CPAP Systems

The CPAP system functions primarily to regulate gas flow during inhalation and exhalation and to maintain a consistent pressure at the nasal airway opening. The CPAP system consists of 4 intermediate components, including a heated/humidified blended gas source, a nasal interface, a

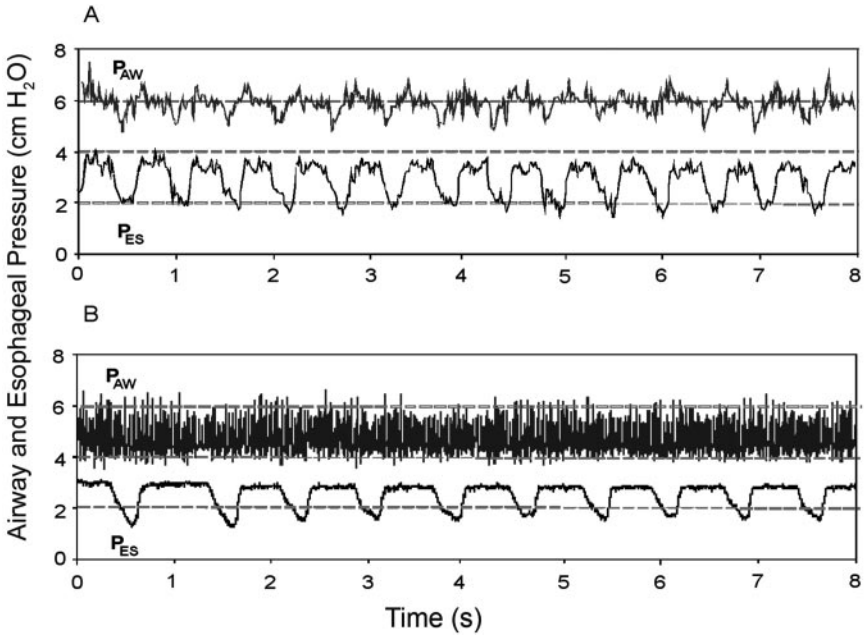

Fig. 3. Airway pressure (P_{AW}) and esophageal pressure (P_{ES}) tracings obtained during (A) ventilator nasal CPAP (constant pressure) at 6 cm H_2O CPAP, and (B) bubble nasal CPAP (variable pressure) at 5 cm H_2O. Note the variation in the airway pressure related to patient efforts during ventilator CPAP, and by the noisy component of gas bubbling through the water-seal chamber during bubble CPAP.

patient circuit and the pressure-generation apparatus. The CPAP system also provides a means for monitoring and limiting the airway pressures.[59] Because of the high level of gas flow generated within these systems, the humidifier should be adjusted to provide a gas that is 100% saturated at a temperature of 37°C.

Nasal interfaces are the devices that provide CPAP to the nasal airway opening. CPAP has been delivered to infants using nasal prongs and masks, bi-nasal pharyngeal tubes, ETTs, naso-ETTs, pressurized plastic bags, head-box enclosures, and tight-fitting face masks.[60] Today the most common nasal interfaces used for delivering CPAP are "short" bi-nasal prongs and nasal masks. Bi-nasal prongs are less invasive and provide the least amount of resistance to gas flow, and, hence, lower imposed (or resistive) WOB.[60] Bi-nasal prongs also facilitate mobilization and oral feeding.[61] In recent meta-analyses, devices using short bi-nasal prongs were found to be more effective than using single naso-pharyngeal prongs in reducing the rate of re-intubation in premature infants supported with CPAP.[62] Nasal masks may provide additional benefits over bi-nasal prongs, since they do not reduce the inner diameter of the nares; however, in vitro and in vivo studies are needed to determine these differences.

CPAP systems have traditionally been classified by the technique used to control the gas flow to the patient. For instance, bubble CPAP is a "constant flow" device because the flow is set by the clinician, and pressure is regulated by some other mechanism (ie, tubing placed within a water-seal column).[7] Devices that use fluidic control to maintain CPAP have been described as "variable flow" devices. Although these devices operate at set constant flows, mechanisms within the CPAP pressure fluidic generator allow for additional gas delivery to the patient in order to maintain a consistent airway pressure. Ventilator CPAP has been considered a "constant flow" device because the exhalation valve regulates the CPAP level, and the flow is set by the clinician. However, recent technological improvements in infant ventilator design can allow a variable gas flow from a demand valve within the ventilator. In most cases the CPAP level is not maintained at an absolute "constant" pressure level, and fluctuations in the airway pressure are common. For instance, ventilator CPAP is often considered a "constant" pressure CPAP; however, the airway pressure profile can vary in response to the patient inspiratory and expiratory efforts and/or the ventilator's ability to servo-control the gas delivery. During bubble CPAP the airway pressure oscillates around the mean airway pressure because of the bubbling of gases through a liquid, and this device has been classified as a "variable" pressure CPAP system. Figure 3 shows tracings of airway pressure and esophageal pressure tracings in 2 subjects breathing spontaneously during ventilator CPAP (see Fig. 3A) and bubble CPAP (see Fig. 3B).

Currently, there is a lack of experimental data to suggest that any one CPAP system is superior to another for improving outcomes. The clinician's abilities to assess the system, assure safety, and respond to changes in the patient's

pathophysiologic condition far outweigh the brand or method used to generate and deliver CPAP. Table 1 is a summary of the literature comparing differences in outcomes variables related to the use of different CPAP systems.

Ventilator Nasal CPAP

In the 1970s a CPAP system consisting of a constant-flow gas system and a spring-loaded positive end-expiratory pressure (PEEP) valve (flow resistor) was commonly applied to infants.[63] With the introduction of neonatal mechanical ventilators, in the mid-1970s, CPAP administration was made easier, and systems using mechanical PEEP valves were less commonly used. The widespread use of ventilator CPAP (often referred to as "conventional CPAP") is still favored as a simple and efficient method for providing CPAP to infants.[64] Ventilator CPAP is a variable or constant flow, constant-pressure system. Today, several microprocessor-controlled infant ventilators incorporate specific noninvasive CPAP modes designed to deliver CPAP to infants. In some cases, software algorithms provide rapid servo-controlling between the demand-flow system and the expiratory valve to regulate the CPAP level. For example, if the patient has a high peak-flow requirement, the demand valve will open to meet this flow requirement, and if the patient coughs or has a forced exhalation, pressure is sensed in the ventilator and the exhalation valve opens to release excessive pressure beyond the set CPAP level. Ventilator CPAP may also provide leak compensation features, apnea back-up breaths, and airway graphics monitoring. Another advantage of ventilator CPAP is that following extubation the device is readily available for CPAP at the bedside. The major limitation to these systems is that the pressure monitoring and pressure regulating mechanism is usually located back at the ventilator and not at the patient interface, which may make ventilator CPAP less responsive to the extremely small patient efforts, especially when large airway interface leaks are present. Commonly used nasal interfaces for ventilator CPAP include Hudson (Hudson RCI, Research Triangle Park, North Carolina) and Argyle (Covidien, Mansfield, Massachusetts) bi-nasal prongs.

Fluidic Control Nasal CPAP

Fluidic control CPAP is achieved by controlling the system fluid dynamics with non-moving valves that apply several fluidic principles of operation at the patient nasal interface. The operational characteristics are similar to a fluidic device that was used in Scandinavia to provide CPAP to infants for nearly 2 decades.[65] Fluidic control systems are further classified as variable-flow or constant-pressure generating devices. The proposed mechanisms of fluidic control systems are to provide adequate inspiratory flow, maintain stable pressure at the airway opening, and thus maintain a more consistent end-expiratory lung volume. Fluidic control CPAP systems maintain a low level of imposed WOB and allow rapid transition from inhalation to exhalation (approximately 4 ms),[66] thus minimizing exhalation against the flow of incoming gases. Based on the patient demand, 2 separate flow pathways are created during inhalation and exhalation at the nasal airway opening. This allows rapid flow response during inhalation and unimpeded flow through an open pathway during exhalation. These factors may have important clinical implications for improving patient comfort and stabilizing lung function in infants with weak respiratory efforts and leaky nasal interfaces.

Infant Flow. The Infant Flow nasal CPAP system (Cardinal Health, Dublin, Ohio), formerly known as the Aladdin 1, is a form of fluidic control CPAP that was first described by Moa and colleagues in 1988.[67] The Infant Flow CPAP system consists of a flow driver (Fig. 4A), which provides a continuous blended gas source, and an airway pressure monitoring system. The flow adjusted to 8 L/min generally results in a CPAP level of 5 cm H_2O.[68] The flow driver is connected to the Infant Flow generator (see Fig. 4B) using a proprietary heated-wire circuit. The flow generator is connected to silicone nasal prongs (see Fig. 4C) or nasal mask (see Fig. 4D) to interface with the patient. It has been proposed that the thin, soft material that is used to construct the nasal prongs flares out during gas inflow, thus increasing the effective internal diameter and decreasing the potential for leakage around the prongs.[69] The Infant Flow generator houses 2 gas injectors (1 per nare) and a fluidic flip valve system (Fig. 5.)

With no spontaneous breathing occurring (steady state), the gas injectors in the flow generator receive gas from the flow driver. The gas is then nozzled continuously through the restrictive gas injectors, accelerating the gas, forming a gas jet directed toward the nasal airway.[70] As the gas leaves the injector and enters the prongs, it loses velocity, which, in turn, causes a rise in pressure (CPAP). According to the Bernoulli principle, "the energy in a flowing gas is maintained and, as a consequence, a reduction in velocity results in a rise in pressure."[71] Additional gas from the injector leaves the system or accumulates in the exhalation tube circuit, which is always open to the atmosphere. When the patient initiates an inhalation, gas is made available by the gas injectors. If the flow requirements of the patient exceed the available gas flow from the injectors, the combination of jet mixing and the Coanda effect allows additional gas particles to be entrained from the exhalation tubing to maximize gas delivery to the patient. Upon exhalation, the pressures exerted in the nasal cavity by the patient's effort cause the gas jet to "flip" and redirect incoming flow from the jet toward the exhalation tube, and thus the patient's exhaled gases pass unimpeded through

Table 1. Experimental Data Comparing CPAP Systems

First Author	Year	Study Design	Sample Subjects	*n*	Systems Compared	Objective(s)	Summary of Outcomes
Klausner[68]	1996	In vitro, bench	Infant test-lung model	NA	Infant Flow CPAP vs variable resistor (nasal prongs)	Compared differences in the level of imposed WOB	Imposed WOB was 4 times greater using the variable resistor ($P < .01$).
Lee[89]	1998	In vivo, human	Premature infants; birth weight < 2,000 g	10	Bubble CPAP (ETT) vs ventilator CPAP (ETT)	Compared differences in gas exchange, tidal volume, and respiratory rate	Infants supported with bubble CPAP had lower minute volume ($P < .001$) and respiratory rate ($P = .004$).
Nilsson[103]	1999	In vitro, bench	Infant test-lung model	NA	Infant Flow CPAP vs Arabella CPAP	Compared differences in dynamic airway pressure stability	There was greater pressure stability using the Infant-Flow CPAP device than with the Arabella CPAP.
Mazzella[76]	2001	In vivo, human	Premature infants	36	Infant Flow CPAP vs bubble CPAP (neonatal/pediatric-ETT)	Compared differences in successful extubation and oxygen requirement	Oxygen requirement and respiratory rate were lower in infants supported with Infant-Flow CPAP ($P < .001$).
Hückstädt[73]	2003	In vivo, human	Newborn infants (< 40 wk gestational age)	20	Ventilator CPAP (neonatal/pediatric-ETT) vs Infant Flow CPAP	Compared differences in tidal breathing variables and airway pressure fluctuations to determine the stability of CPAP	The CPAP fluctuations were lower ($P < .05$) and peak flow and tidal volumes were higher ($P < .05$) in infants supported with the Infant-Flow CPAP system.
Stefanescu[74]	2003	In vivo, human	Premature infants; ≤ 1,000 g	104	Infant Flow CPAP vs ventilator CPAP (nasal prongs)	Compared differences in the extubation failure rate (re-intubation within 7 d of initial extubation), chronic lung disease, and mortality	Infants supported using Infant-Flow CPAP had fewer days on supplemental oxygen ($P = .03$) and shorter hospital stay ($P = .02$).
Courtney[80]	2003	In vivo, human	Premature infants; birth weight < 1,500 g	8	Infant Flow CPAP vs Arabella	Compared differences in lung-volume recruitment, WOB, respiratory rate, and lung compliance at different CPAP levels	There were no significant differences in any of the variables tested comparing these systems.
Buettiker[75]	2004	In vivo, human	Newborn infants; < 28 d following delivery	8	Ventilator CPAP (neonatal/pediatric ETT) vs ventilator CPAP (nasal prongs) vs Infant-Flow CPAP	Compared differences in skin breakdown, air leak, and duration of treatment	Duration of CPAP was lowest in the Infant-Flow CPAP group ($P < .05$).
Pandit[77]	2004	In vivo, human	Premature infants; birth weight < 1,800 g	24	Infant Flow CPAP vs ventilator CPAP (nasal prongs) vs modified nasal cannula	Compared physiologic differences in outcomes using 2 CPAP devices and a nasal cannula	Tidal ventilation and lung volumes were greater with Infant-Flow CPAP ($P < .001$). The resistive and inspiratory WOB was lower in infants supported with Infant-Flow CPAP than ventilator CPAP ($P < .05$).
Lipsten[42]	2005	In vivo, human	Premature infants; birth weight < 1,500 g	18	Infant Flow CPAP vs bubble CPAP	Compared differences in WOB and breathing asynchrony (phase angle) at different CPAP levels	Resistive WOB ($P = .01$), respiratory rate ($P = .03$), and phase angle ($P = .002$) were greater in infants supported by bubble CPAP.
Chan[85]	2007	In vivo, human	Premature infants; birth weight < 1,500 g	45	Bubble CPAP vs ventilator CPAP	Compared differences in respiratory and non-respiratory clinical outcomes	Duration of CPAP ($P = .004$) and the number of days without substantial apnea during CPAP ($P = .03$) were lower in the group supported with bubble CPAP.
Pillow[88]	2007	In vivo, animal	Premature lambs	34	Bubble CPAP vs ventilator CPAP	Compared differences in gas exchange physiology and lung injury, and to determine if the applied flow influences short-term outcomes	Lambs supported with bubble CPAP had greater area under the flow-volume curve at both 8 L/min ($P = .004$) and 12 L/min ($P = .01$), less ventilation inhomogeneity ($P = .02$) and alveolar protein ($P = .01$), extracted a greater amount of the inspired oxygen ($P = .04$), had a lower respiratory quotient ($P = .005$), and maintained a lower P_{aCO_2} and a higher pH ($P = .008$) at 120–150 min.
Hua[97]	2006	In vivo, animal	Juvenile rabbits	12	Bubble CPAP vs ventilator CPAP	Compared difference in exhaled nitric oxide levels	Exhaled nitric oxide level was lower during bubble CPAP support ($P < .001$).
Huang[87]	2008	In vivo, animal	Juvenile rabbits	12	Bubble CPAP vs ventilator CPAP	Compared differences in blood gases and vital signs	Blood pressure was higher during ventilator CPAP ($P = .02$). There were significant differences in respiratory rate, pH, and P_{aO_2}, with corresponding increases in the P_{aCO_2} and HCO_3 during ventilator CPAP from baseline, which were not different using bubble CPAP.
Gupta[98]	2009	In vivo, human	Premature infants; 24–29 wk gestational age	141	Bubble CPAP (nasal prongs) vs Infant-Flow CPAP	Compared differences in successful extubation, duration of support, chronic lung disease, and other complications	Extubation failure rate was lower in infants supported with bubble CPAP ($P = .046$). The duration of support was shorter in the bubble CPAP group ($P = .03$).

CPAP = continuous positive airway pressure NA = not applicable WOB = work of breathing ETT = endotracheal tube

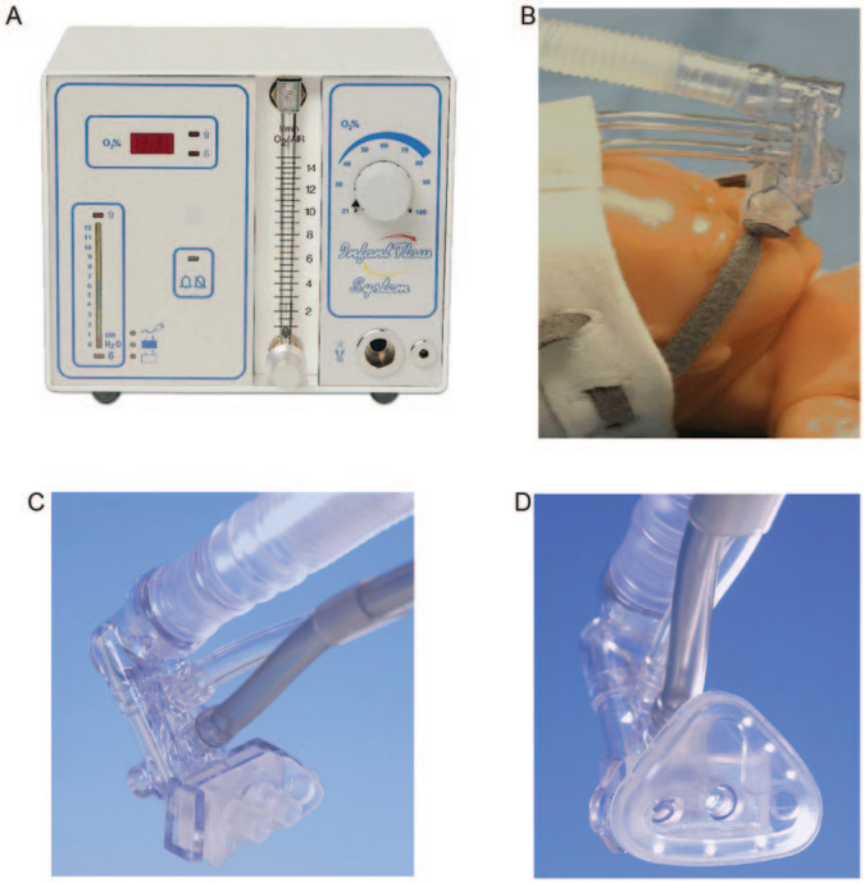

Fig. 4. The Infant Flow continuous positive airway pressure (CPAP) system. A: The Infant Flow driver. B: Infant Flow generator. C: Nasal prongs. D: Nasal mask. (Courtesy of Cardinal Health.)

the exhalation tube to the atmosphere. When the expiratory breathing effort stops, the jet flips back to the inspiratory position.[72] Figure 6 shows a schematic of the Infant Flow generator and visual representation of these fluidic principles.

Experimental data from bench and clinical studies have shown that Infant Flow CPAP is capable of providing a consistent airway pressure[71,73] and has also been shown to impose a lower WOB[68] than do other devices that use fluidic control to maintain CPAP. Stefanescu et al managed infants post-extubation using either Infant Flow CPAP or ventilator CPAP. The group supported with Infant Flow CPAP had fewer days on supplemental oxygen ($P = .03$) and shorter hospital stay ($P = .02$).[74] Buettiker et al found that Infant Flow CPAP resulted in a shorter duration of support than did ventilator CPAP.[75] Mazzela et al showed that infants supported with Infant Flow CPAP had lower oxygen requirements and respiratory rates ($P < .001$) than did infants supported with bubble CPAP.[76] In another study, Lipsten et al found that infants supported with Infant Flow CPAP had lower resistive WOB ($P = .01$), respiratory rate ($P < .03$), and phase angle ($P = .002$) than did infants supported with bubble CPAP.[42] Pandit et al found that infants supported with Infant Flow CPAP had greater tidal ventilation and lung volumes ($P < .001$), and the resistive and inspiratory WOB was lower ($P < .05$) than in infants supported with ventilator CPAP.[77]

The Infant Flow SiPAP ("sigh" positive airway pressure) (Cardinal Health, Dublin, Ohio) is a relatively new noninvasive device that is being used more frequently in the neonatal intensive care unit (NICU) setting. The Infant Flow SiPAP uses the same Infant Flow generator and fluidic principles as the Infant Flow CPAP but incorporates a newly designed flow driver (Fig. 6). The major difference from CPAP is that SiPAP allows the infant to breathe spontaneously at 2 separate CPAP levels (see Fig. 6). The secondary CPAP level is generally set 2–3 cm H_2O higher than the baseline CPAP pressure, the "Time-High" (ie, inspiratory time) 1–3 seconds and the respiratory rate controls the frequency and duration of the intermittent "sigh" breaths.[72] The goal of Infant Flow SiPAP is to enhance alveolar recruitment, improve gas exchange, and provide airflow stimulation using sighs to prevent apnea requiring intubation. Outside of the United States, Infant Flow SiPAP allows patients to trigger SiPAP breaths using an applanation capsule attached to the abdomen. However,

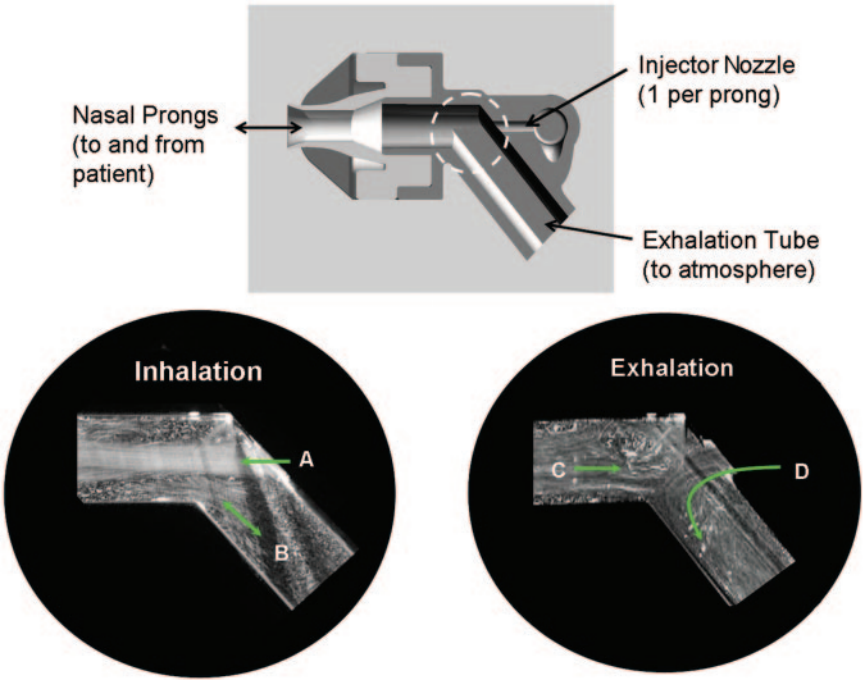

Fig. 5. Infant Flow generator schematic and gas flow dynamics during inhalation and exhalation. (Modified with permission from Cardinal Health.) The top picture shows the generator, and the white dashed circle shows the gas flow pathway within the generator illustrated in the circular figures below. These sections have been enlarged to show the fluid dynamics during inhalation and exhalation. With no spontaneous breathing (steady state), the gas injector nozzle accelerates a gas jet (A) to provide a constant pressure level (Bernoulli effect), and additional gas leaves the system through the exhalation tube (B). When the patient initiates an inspiratory effort the generator converts kinetic energy from jet mixing by the gas jet (A), and flow is shifted from the exhalation tubing (B) and also delivered to the patient (Coanda effect). Upon exhalation, the pressures exerted in the nasal cavity by the patient's efforts (C) cause the gas jets to "flip" toward the exhalation tube (D), and exhaled gas flow and jet flow leave the generator, unimpeded, through the exhalation tube and to the atmosphere. When the expiratory breathing effort stops, the jet flips back to the inspiratory position (A).

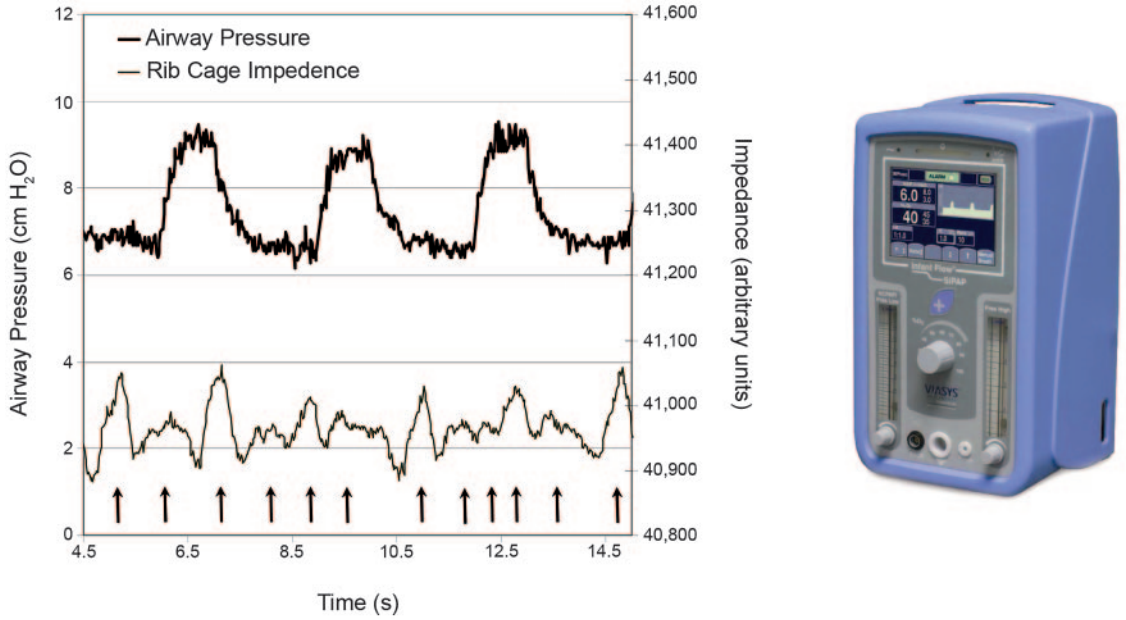

Fig. 6. Infant Flow SiPAP ("sigh" positive airway pressure) nasal continuous positive airway pressure system. Left: Airway pressure scalar and rib-cage impedance measurements obtained from a premature infant supported with the biphasic mode The arrows indicate patient-initiated breaths. (From Reference 72, with permission.) Right: The Infant Flow SiPAP driver (Courtesy of Cardinal Health.)

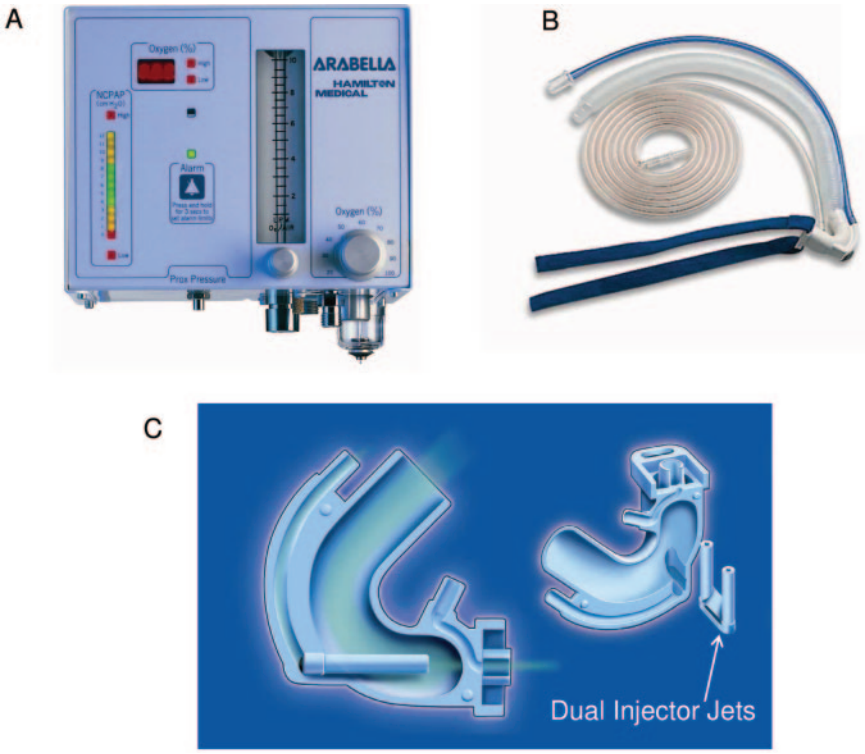

Fig. 7. The Arabella continuous positive airway pressure (CPAP) system. A: Monitoring gas mixer. B: Universal generator and circuit. C: Schematic of the universal flow generator. (Courtesy of Hamilton Medical.)

the rise in pressure from the baseline CPAP level to the secondary CPAP level is gradual, making the breath delivery different from the pressure profile provided by pressure-support ventilation found on ventilators. Infant Flow SiPAP has been shown to result in significant improvements in gas exchange from that observed with standard nasal CPAP in preterm infants.[78] Clinical research is currently being performed to evaluate this method's impact in outcomes in infants with respiratory disease.

Arabella. The Arabella nasal CPAP system (Hamilton Medical, Reno, Nevada), formerly known as the Aladdin 2, also uses fluidic control mechanisms to maintain a consistent CPAP and provide unimpeded exhalation to atmosphere. The Arabella CPAP system monitoring gas mixer (Fig. 7A) provides a blended gas source and allows pressure monitoring. Gas is delivered through a proprietary delivery circuit (see Fig. 7B), and the universal generator (see Fig. 7C) attaches to soft nasal prongs or a nasal mask.

The major difference with the Arabella from other fluidic devices is that the jet injectors extend partway into the universal generator chamber and exhaust into a larger cavity, whereas the Infant Flow CPAP gas injectors are flush with a wall. The geometric angles for guiding flow pathways are also different (see Fig. 7C).[66] At steady state the dual injector jets produce an air jet directed at the nasal airway, and CPAP is generated by the Bernoulli effect. During inhalation the dual injector jets provide 130 mL of volume per second.[79] If the patient's flow exceeds this value, then additional gas can be entrained using the Venturi principle and the Coanda effect. "Upon exhalation, flow beyond the 2 gas portals (distal to the gas injectors) enters into a low pressure area with minimal back pressure and therefore results in a decrease in the velocity of the airflow, allowing the flow to reverse its direction."[79] This unique pressure "flow stalling" technique allows infants to exhale passively to an open exhalation pathway and still maintain a consistent pressure level at the nasal airway.

In a study by Courtney et al comparing the Infant Flow CPAP system to the Arabella in low-birth-weight infants, no differences were observed in lung volume recruitment ($P = .47$) or in resistive WOB ($P = .61$) between devices. Compliance, tidal volume, respiratory rate, and minute ventilation were also similar.[80]

AirLife. The AirLife system (Cardinal Health, Dublin, Ohio) is a new form of CPAP designed to help reduce WOB during inhalation and exhalation and provide a consistent airway pressure. The level of CPAP created is proportional to the flow provided by the driver, and the relationship is very similar to the Infant Flow CPAP device

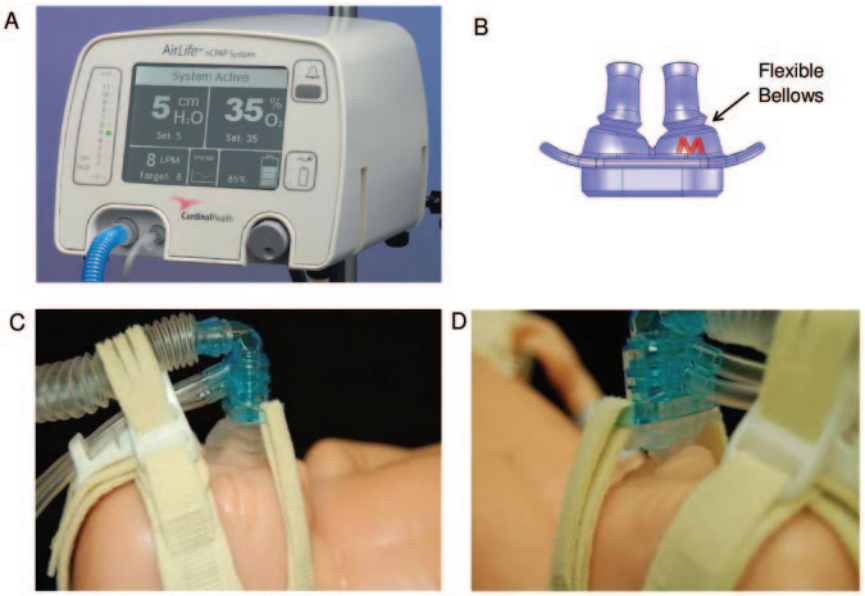

Fig. 8. The AirLife continuous positive airway pressure system (CPAP). A: The flow driver. B: Nasal prongs. C: Flow generator and nasal mask. D: Flow generator and nasal prongs. (Courtesy of Cardinal Health.)

(eg, 8 L/min of flow provides approximately 5 cm H_2O CPAP). When using the AirLife CPAP "flow driver" (Fig. 8A), the caregiver sets the CPAP level and the flow driver automatically adjusts the flow to deliver the desired CPAP level. The servo-controlling mechanism for flow adjustment is based on feedback obtained from the proximal pressure line attached at the flow generator (see Figs. 8C and 8D). The flow driver is also designed to compensate automatically for leaks that may occur at the patient interface due to an imperfect fit or as the baby moves. This feature provides a consistent airway pressure and minimizes nuisance alarms. If the leaks are temporary and subsequently resolved, then the flow driver will automatically reduce the flow to maintain the set CPAP. The nasal prongs are specially designed to provide optimal fit using tapered prongs with flared tips for a gentle seal, and flexible bellows designed to self-align and reduce torque on the nasal anatomy (see Figs. 9B and 9D). Nasal masks with a flexible bellows can also be used with this system (see Fig. 8C).

The proposed mechanisms of the AirLife CPAP system function are based on similar fluidic principles as the Infant Flow CPAP system. Two low-momentum jets per nare impinge inside the flow generator to form a stable jet pump. The jet pumps exert a force on the nasal airway, providing a consistent pressure level. During inhalation, if the patient's peak inspiratory flow exceeds the flow provided by the jets, then the generator's jet pumps efficiently increase the delivered flow to match the demand and provide a stable CPAP level. As the patient begins to exhale (and throughout the expiratory phase), the low-momentum jets are easily deflected away from the impingement point, disrupting the jet pump and the pressure it exerts. As the jets disrupt, they shed vortices that spiral outward, combining with the patient's exhaled gases to create an organized, efficient flow path toward the exhaust ports. Vortice shedding also helps to reduce the imposed WOB during exhalation by minimizing expiratory flow resistance (Fig. 9).

Bubble Nasal CPAP

Bubble CPAP is constant-flow, variable-pressure CPAP system. Jen-Tien Wung of Children's Hospital of New York, Columbia University, is often accredited with its development, using bi-nasal prongs. Further, this form of support, as mentioned previously in the history section, was described using Von-Tiegel's apparatus with a face mask, nearly a century ago.[18,19] Nekvasil and colleagues were the first to publish their findings using bubble CPAP in a small series of intubated infants.[81] There is great interest in this form of CPAP support worldwide, mainly because it is simple to operate, inexpensive, safe, and has been shown to be effective in maintaining CPAP in premature infants.

The bubble CPAP system consists of a blended, humidified gas source (4–6 L/min) attached to nasal prongs (Fig. 10A) by a length of inspiratory circuit. A pressure manometer and/or pressure pop-off is attached to the nasal prongs' interface. A separate length of expiratory circuit tubing is attached from the nasal interface, thus allowing egress of exhaled gases and system bias flow into a water-seal column of sterile H_2O/0.25% acetic acid mixture. The CPAP level is determined by the distance the distal end of

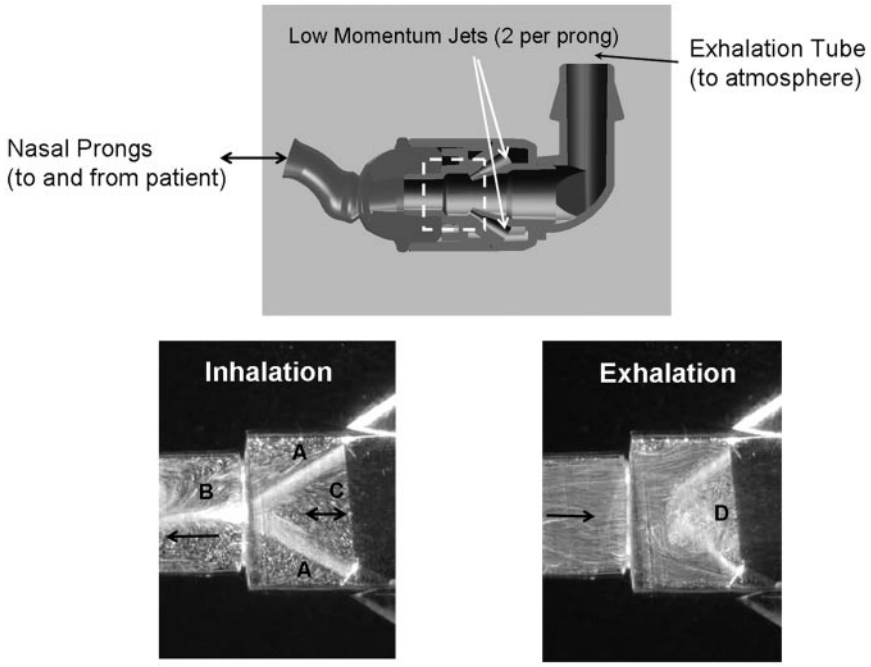

Fig. 9. AirLife flow generator schematic and gas flow dynamics during inhalation and exhalation The dashed square area represents the 2 figures illustrating system gas flow dynamics during inhalation and exhalation (below). During inhalation, 2 low-momentum jets (A) per nare impinge inside the flow generator to form a stable jet pump (B). The jet pumps exert a force on the nasal airway, providing a consistent continuous positive airway pressure (CPAP) level. During inhalation, if the patient's peak inspiratory flow exceeds the flow provided by the jets, then the generator's jet pumps efficiently deliver more flow to match the demand and provide a stable CPAP level (C). As the patient begins to exhale (and throughout the expiratory phase), the low-momentum jets are easily deflected away from the impingement point (D), disrupting the jet pump and the pressure it exerts. As the jets disrupt, they shed vortices that spiral outward, combining with the patient's exhaled gases to create an organized, efficient flow path toward the exhalation tube. (Courtesy of Cardinal Health.)

the expiratory tubing is placed below the water-seal surface (5 cm below surface = 5 cm H_2O). A tape measure can be attached to the side of the water-seal to help determine this setting. However, the CPAP level is highly flow-dependent, due to flow resistive elements within the bubble CPAP system, and, thus, higher flow settings result in higher CPAP levels than those intended by the submersion distance depth setting.[82,83] The practice of monitoring the airway pressure at the nasal interface using an attached pressure manometer provides a more accurate reflection of the delivered CPAP level.

In the United States, centers have begun implementing home-made bubble CPAP systems into the clinical setting using equipment modified from supplies that are typically found in many hospitals' respiratory care equipment storage areas (see Fig. 10B). Because of the low cost of maintenance, simplicity, and no need for an electrical power source, these devices are also frequently used to support patients in resource-limited settings.[84-86] Outside of the United States, a commercially available bubble CPAP generator (see Fig. 10C) has been developed for use in infants and is currently awaiting Food and Drug Administration approval in the United States.

The variability in the airway pressure waveform (see Fig. 4B) created during bubble CPAP has stimulated a tremendous amount of interest, and recent research suggests that there may be additional benefits for using bubble CPAP over devices that strive to maintain a constant pressure level at the airway.[87] As a result of the gas flowing through the expiratory circuit into the water-seal column, high-frequency small-amplitude pressure oscillations (approximately 2–4 cm H_2O at dominant frequencies of 5–20 Hz and 40–100 Hz)[88] are generated by bubbles and are transmitted back into the patient's lungs. Lee et al made the observation that the chest walls of intubated infants vibrate during bubble CPAP at a similar rate to high-frequency oscillatory ventilation.[89] It has been proposed that the pressure oscillations that are transmitted to the nasal interface and superimposed on the patient's natural breathing pressure provide effects similar to high-frequency oscillatory ventilation for improving interregional gas mixing and alveolar recruitment.[90,91]

Versmold et al evaluated the P_{aCO_2} responses of bubble CPAP in tracheotomized, chemically paralyzed animals. They found that animals placed on bubble CPAP had a markedly slower apneic increase in P_{aCO_2} than did animals

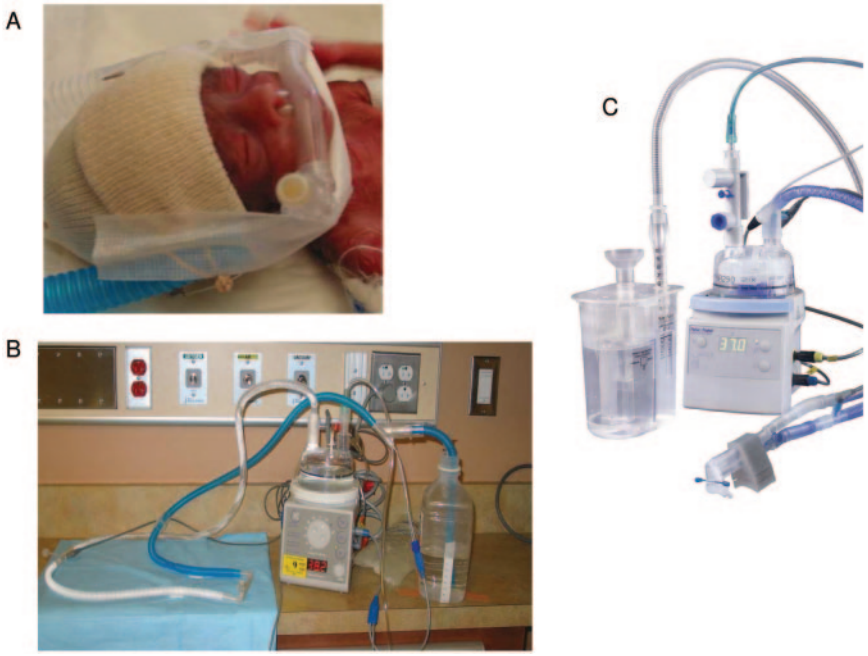

Fig. 10. Bubble nasal continuous positive airway pressure (CPAP) systems. A: A premature infant with Hudson nasal prongs and a chin strap to help prevent pressure leakage. (Courtesy of Rose DeKlerk, Vermont Oxford Network.) B: A homemade bubble CPAP setup using ventilator circuits, humidifier, and a sterile water bottle (with a tape measure used to determine the level of the expiratory (distal) tubing. (Courtesy of Rose DeKlerk, Vermont Oxford Network.). C: Fisher & Paykel Healthcare bubble CPAP system, comprising CPAP generator (currently available only outside of the United States), humidifier, and nasal prongs. (Courtesy of Fisher & Paykel Healthcare.)

receiving ambient pressure and ventilator-derived CPAP.[92] These results suggest that measurable ventilation effects created by the pressure oscillations of the bubble CPAP system do exist with this CPAP system. Results from these animal studies are further supported by clinical research demonstrating lower respiratory rates ($P = .004$) and minute volume ($P < .001$) in intubated infants supported with bubble CPAP than with ventilator CPAP.

The magnitude and bandwidth of the oscillatory pressure fluctuations, generated at the airway interface, can be augmented by increasing the system bias flow setting; however, experiments evaluating gas-exchange and ventilation effects, following increasing the system flows during bubble CPAP, have not demonstrated that this practice results in any physiologically important benefits in spontaneously breathing[93,94] and muscularly paralyzed subjects.[95]

In a bench study using a simulated infant test lung model, Pillow et al demonstrated that the magnitude and frequency of mechanical pressure oscillations transmitted to the lung model were greater when the compliance of the lung model was lower.[88] This implies that a higher level of support may automatically be achieved in patients who have deteriorating lung mechanics. A limitation of this study was that no airway leak was incorporated into the model, and the delivered pressure oscillations therefore were likely to be higher than what actually occurs in vivo.

Pillow et al used an intubated premature lamb model to compare differences in gas-exchange physiology and lung injury resulting from treatment of respiratory distress with either bubble CPAP or ventilator CPAP, and to determine if the applied pressure oscillations (during bubble CPAP) influences short-term outcomes.[94] Lambs supported with bubble CPAP had greater areas under the flow-volume curves at both 8 L/min ($P = .004$) and 12 L/min ($P = .01$), less ventilation inhomogeneity ($P = .02$) and alveolar protein contents ($P = .01$), extracted greater amounts of the inspired oxygen ($P = .04$), had lower respiratory quotients ($P = .005$), and maintained lower P_{aCO_2} and higher pH ($P = .008$) at 120–150 min than did animals supported by ventilator CPAP. They attributed these improvements to the addition of superimposed pressure oscillations during bubble CPAP that may augment alveolar recruitment and stabilize the lungs through a phenomenon known as "stochastic resonance." Stochastic resonance has been described as the process of adding "noise" to a weak input signal to enhance the output in a non-linear system.[96] There is some speculation that the benefits in lung recruitment observed with bubble CPAP can reduce lung injury and inflammation.[97] Controversy exists over whether the noisy component of pressure oscillations created by bubble CPAP would have similar effects when applying

leaky nasal prongs to infants with respiratory distress. The majority of the previously mentioned studies have been conducted only in endotracheally intubated subjects, and these findings therefore cannot be extrapolated so readily to infants supported during bubble CPAP using nasal prongs.

In a recent randomized controlled trial, Gupta et al evaluated the efficacy and safety of bubble CPAP compared with the Infant Flow CPAP system for the post-extubation management of preterm infants with RDS.[98] Infants were randomized to bubble CPAP ($n = 71$) and Infant Flow CPAP ($n = 69$) and were managed using a standardized protocol. Extubation failure rate was lower ($P = .046$) and the duration of support was shorter ($P = .03$) in infants ventilated < 14 days when supported with bubble CPAP following extubation.

The Role of Early Nasal CPAP in Supporting Premature Infants With Respiratory Distress Syndrome

The fragile lungs of premature infants affected with RDS are typically stiff, underdeveloped, surfactant-deficient, fluid-filled, and prone to alveolar atelectasis and airway collapse. Endotracheal intubation and mechanical ventilation are frequently indicated for severe respiratory failure, placing premature infants at greater risk of destabilization and developing severe complications. Ventilator-induced lung injury is created by excessive end-inspiratory lung volume (volutrauma) and repetitive opening and closing of terminal lung units due to insufficient end-expiratory pressure (atelectrauma), propagating the release of pro-inflammatory markers (biotrauma) in the lungs.[99-102] Compelling experimental data indicate that even short-term exposure to excessive delivered tidal volume during ventilation can exacerbate lung injury[103,104] and compromise the therapeutic effect of surfactant-replacement therapy.[105] Mechanical ventilation and high fraction of inspired oxygen (F_{IO_2}) superimposed on the premature lung have been implicated as major causes of infants developing CLD.[106-108] The initial inflammatory response, repair mechanisms, and continued exposure to ventilator-induced lung injury, as well as oxidants generated during prolonged oxygen administration, arrest postnatal lung development and pulmonary capillary angiogenesis,[53,109-111] resulting in alveolar simplification, interstitial fibroproliferation, airway lesions, and decreased surface area for gas exchange.[112,113]

The severity of CLD ultimately determines the clinical course for prolonged oxygen and ventilation requirements.[114] CLD is defined by an oxygen requirement at 36 weeks (postmenstrual age).[112] The incidence of CLD in infants born at < 30 weeks and of very low birth weight (< 1,500 g) is prevalent; however, the severity of CLD in infants is decreasing.[114] Approximately 20–25% of premature infants who survive the neonatal period develop major impairments in neurological developments, including deafness, blindness, and cerebral palsy.[115] The majority of adolescents and young adults surviving CLD have reactive airway disease, characterized by airway obstruction, bronchiolar hyper-reactivity, and hyperinflation.[116] CLD is the most common chronic lung disease of infancy in the United States and is a major economic burden on the health-care system, ranking second in health-related expenditures for chronic respiratory-related illnesses in pediatrics.[117]

The respiratory approach used in the initial stages of extra-uterine life may play a large role in determining outcomes in premature infants, but a definitive approach still remains elusive. The use of mechanical ventilation has saved many lives; however, there is a general consensus that brief exposure to mechanical ventilation in premature infants is preferable for reducing the incidence of CLD, and this concept has not been widely adopted into clinical practice. CPAP is frequently considered a gentler form of lung support for premature infants. By avoiding intubation, the airways can be protected from mechanical injury and colonization related to the ETT.[118] Infants breathing spontaneously during CPAP also require less sedation than infants breathing spontaneously during mechanical ventilation. Evidence suggests that the resistive load imposed by ETTs,[119,120] ventilator demand valves,[121,122] and exhalation valves[123,124] may add to causal respiratory failure, which may also help to explain why it is not unusual to register a decreased P_{aCO_2} in infants following extubation from ventilator-derived CPAP via ETT.[125]

The initial respiratory strategy for supporting infants varies substantially from hospital to hospital, as do outcomes related to these practices. Some of the most challenging decisions that clinicians are faced with pertain to the timing for implementing CPAP or whether this approach should be modified based on gestational age or birth weight. This concept is further complicated by the timing of surfactant-replacement therapy and whether the risks of intubation and mechanical ventilation, for administration purposes, might outweigh the benefits of its use in the smallest of patients. These factors pose some of the most perplexing questions of modern-day neonatology and are currently focused within an area of intense clinical research.

A large multicenter randomized controlled trial is currently being performed by the Vermont Oxford Network. This study, entitled "Delivery Room Management Trial," will compare outcomes in premature infants supported using 3 common initial approaches in post-delivery care. These practices include: intubation, prophy-

lactic surfactant administration shortly after delivery, and subsequent stabilization on ventilator support; early stabilization on CPAP with selective intubation and surfactant administration for clinical indications; and intubation, prophylactic surfactant administration shortly after delivery, and rapid extubation to CPAP.[126]

For the purpose of this review, I will discuss two of the most common clinical approaches that are currently used for supporting premature infants with CPAP, including elective early CPAP directly following birth, and CPAP following extubation from mechanical ventilation. This discussion will then summarize research findings to determine whether these disparate practices have any effects on outcomes associated with prematurity.

Early Nasal CPAP Following Birth

CPAP use following birth has traditionally been described for supporting infants who are failing oxygen therapy and has been implemented as a "rescue" strategy to reduce intrapulmonary shunting and improve arterial oxygenation. This approach applies CPAP only once the patient begins to show signs of deteriorating oxygenation, as indicated by $P_{aO_2} < 50$ mm Hg on $F_{IO_2} > 0.4–0.5$ measured over a discrete time period (30 min).[127,128] Elective early nasal CPAP (early CPAP) or "prophylactic" CPAP is a minimally invasive approach that embraces the initial early use of CPAP in spontaneously breathing premature infants and is generally not preceded by supplemental oxygen therapy or endotracheal intubation.

Early CPAP commences within 5–10 min following birth and/or following resuscitation and stabilization of the infant in the delivery room.[129,130] Early CPAP is intended to serve as an alternative to intubation and mechanical ventilation in infants of all sizes and gestational ages, irrespective of the clinical respiratory status. It has been proposed that initial application of early CPAP in infants may have the following advantages: prompt stabilization avoids deterioration; avoids or decreases exposure to high F_{IO_2}; shortens ICU stay; and decreases need for intubation.[63] Thus, the goals of early CPAP are to minimize intubation and mechanical ventilation to reduce complications related to this approach.

It has been postulated that, by applying CPAP at birth the lungs are not initially injured, and, therefore, "if injury can be minimized, then less surfactant should be needed."[54] In the case of early CPAP the risks associated with endotracheal intubation and mechanical ventilation are believed to outweigh the benefit of routine prophylactic surfactant administration. Clinicians often view this approach with some trepidation, because infants who could benefit from timely prophylactic surfactant may not receive surfactant until later in the clinical course. Intubation and surfactant administration are performed only when the infant has first demonstrated "failure" during the clinical course of early CPAP, as indicated by: pH < 7.20; $P_{aCO_2} > 65$ mm Hg; F_{IO_2} requirement > 0.6; and frequent and unresponsive apneas.[131] Some institutions accept lower failure threshold criteria during early CPAP, to assure earlier surfactant administration.

In a retrospective study, Ammari et al evaluated mortality and incidence of CLD in infants supported initially using either intubation/mechanical ventilation or early CPAP.[131] Infants who failed early CPAP, followed by intubation and ventilation, received similar amounts of surfactant (53% vs 51%, odds ratio = 1.1, 95% confidence interval [CI] 1.8–11.4) to the group of infants that was managed initially using mechanical ventilation; however, the mortality rate was lower in the early-CPAP group than in the group supported initially using mechanical ventilation (33% vs 66%, $P < .001$), but the infants non-randomly selected for initial management by intubation/mechanical ventilation were appreciably sicker than the infants in this study in whom early CPAP was initiated, and the mortality and complications were lower in infants failing early CPAP than in the infants intubated and treated with intubation and mechanical ventilation in the delivery room.

The use of initial early CPAP has been referred to as the "Columbia approach," because it was first established by clinicians at Children's Hospital of New York, Columbia University, as the routine initial form of respiratory support for spontaneously breathing premature infants with RDS. The greatest interest in this approach began around 2000, following the publication of 2 separate epidemiologic reports: the first by Avery in the pre-surfactant era,[106] and the second by Van Marter[107] in the post-surfactant era. Avery et al evaluated the differences in CLD rates among 8 centers using historical data from 1,625 low-birth-weight premature infants. The major finding of this analysis was that in one center (Columbia), where CPAP and permissive hypercapnia were used initially to support all premature infants, CLD was almost non-existent (approximately 2% CLD rate), in contrast to the other centers, in which intubation and mechanical ventilation (approximately 15–33% CLD rate) were used as the initial strategy. Van Marter et al performed a retrospective study to determine whether variations in respiratory strategies among 5 medical centers' NICUs might better describe differences in CLD rates in the post-surfactant era.[107] In this case, Columbia had a 4% CLD rate, which again contrasted with a 22% CLD rate in centers that were more likely to use mechanical ventilation and surfactant administration. These data suggest use of CPAP as the predominant choice for initial support, thereby avoiding positive-pressure mechanical ventilation, may play an important role in reducing CLD in infants.

A considerable amount of published data suggest that early CPAP, when used as an initial form of support, is

associated with less need for exogenous surfactant,[132] intubation and mechanical ventilation,[118,133] resulting in a lower incidence of intraventricular hemorrhage[134] and CLD.[132,135,136] However, the majority of these data have been obtained using retrospective study designs comparing historical controls, and the results of these studies should be interpreted with considerable caution. Prospective data obtained from randomized control trials evaluating the clinical benefits of early CPAP are needed. Table 2 reviews prospective and retrospective studies comparing early CPAP to other initial respiratory support strategies used commonly to support premature infants.

In a recent Cochrane meta-analyses, Subramaniam et al sought to determine whether early CPAP following birth is associated with lower rates of mechanical ventilation and CLD than is "rescue" CPAP. This review consisted of only 2 RCTs.[137] In one of the studies cited, nasopharyngeal CPAP (using an ETT) was used, and in the other, nasal prongs were used (CPAP). In these analyses, early CPAP following birth showed no benefit for premature infants. Kugelman et al performed a randomized controlled trial comparing early CPAP to nasal intermittent mandatory ventilation in 43 premature infants (< 35 wk gestational age).[138] Both groups were supported with 6–7 cm H_2O PEEP, and the nasal intermittent-mandatory-ventilation treatment used peak inspiratory pressure of 14–22 cm H_2O. Infants treated with nasal intermittent mandatory ventilation needed less endotracheal intubation than infants treated with early CPAP (25% vs 49%, $P < .05$). Infants treated with nasal intermittent mandatory ventilation also had a lower incidence of CLD than did infants in the early-CPAP group (2% vs 17%, $P < .05$).

Recently, Morley et al published the results of a large international multicenter randomized control trial (COIN trial, *C*PAP *o*r *IN*tubation) in 610 extremely-low-birth-weight infants assigned to receive early CPAP at 8 cm H_2O or intubation/mechanical ventilation at 5 min after birth.[139] The early-CPAP group was intubated for surfactant administration only when predetermined early-CPAP failure/intubation criteria were met. At 28 days of age the unadjusted odds ratio for death or need for oxygen treatment was 0.63 (95% CI 0.46–0.88, $P = .006$), which favored the early-CPAP group; however, no differences were observed between the 2 groups in the combined outcome of death or CLD at 36 weeks. Infants supported with early CPAP initially had a higher incidence of pneumothorax than did infants in the intubation/mechanical ventilation group (9% vs 3%, $P < .001$). This finding may be related to the initial CPAP level used (8 cm H_2O) or that early surfactant-replacement therapy was less likely to be administered in this experimental group.

Early CPAP is possible to initiate in the "smallest" of premature infants and appears to be safe and effective. Results from retrospective and prospective trials do not appear to support or refute clear advantages or disadvantages in the use of early CPAP in these patients. Interestingly, retrospective studies have demonstrated favorable outcomes using early CPAP, whereas prospective randomized controlled trials have not. These findings may be impacted by a number of factors pertaining to changes in practice that can occur in NICUs over time, especially the level of experience and expertise in airway management by clinicians. Aly et al demonstrated that the rate of CLD decreased over a 3-year period following the implementation of an early-CPAP program at one institution (from 46.2% in the first year to 11.1% in the third year, $P = .03$).[140] However, no differences in mortality were observed after the second year, which suggests that acceptance, improved understanding of the airway care technique, and frequency of use of early CPAP over time are relevant factors necessary to provide the highest level of CPAP care. Future prospective trials should consider this transitory period and work to distinguish effects possibly arising from clinicians learning the details essential for the meticulous airway care of infants receiving early CPAP. In the majority of the studies in which mechanical ventilation was used as a control, little to no mention is made of the ventilator strategies used (ie, high-frequency oscillatory ventilation, volume-controlled, or pressure-controlled) or whether the ventilation strategy used a lung-protective approach to minimize ventilator-induced lung injury. Additional studies comparing early CPAP with lung-protective mechanical ventilation are necessary to determine differences in outcomes between these approaches.

Nasal CPAP Following Extubation

CPAP is commonly used to support infants following extubation to minimize risks associated with prolonged exposure to mechanical ventilation and re-intubation.[141-149] Infants extubated from mechanical ventilation are at risk of developing hypoxemia, respiratory acidosis, and apnea. Extubation to CPAP has been associated with a reduction in the need for mechanical ventilation and lower risk of developing CLD in premature infants.[150] CPAP facilitates successful extubation by maintaining airway stabilization, lung volume maintenance, and reducing apnea.[151] In one meta-analysis, Davis and Henderson-Smart evaluated outcomes of randomized control trials comparing CPAP to an oxygen hood to support premature infants following extubation.[151] The results of these analyses suggest that, following extubation, CPAP reduces the incidence of respiratory failure and the need for additional ventilatory support (typical risk ratio 0.62 95% CI 0.51–0.76; typical risk difference −0.17 95% CI −0.23 to −0.10). They also noted that infants supported with 5 cm H_2O did better than did infants supported with CPAP at lower levels.

Table 2. Clinical Studies Evaluating Early Nasal CPAP

First Author	Year	Design	Initial Respiratory Strategy	*n*	Sample Patients	Nasal CPAP Level (cm H_2O)	Nasal CPAP Technique	Summary of Outcomes	Early CPAP-Failure Requiring Intubation (%)
Han[128]	1987	Prospective	Early CPAP vs rescue nasal CPAP	38	< 32 wk gestational age	6	ND	In infants developing RDS, early CPAP had higher F_{IO_2} ($P < .01$) and lower alveolar-arterial oxygen difference ($P < .01$).	Early CPAP 31% Rescue nasal CPAP 40%
Jacobsen[134]	1993	Retrospective	Early CPAP vs intubation/ventilation and CPAP	132	< 33 wk gestational age and birth weight < 1,500 g	6	Benveniste gas-jet valve	Early-CPAP group had less intubation/ventilation ($P < .001$) and had fewer incidences of grade II–IV intraventricular hemorrhage ($P = .01$). The early-CPAP group had a higher rate of septicemia ($P = .045$).	23%
Gitterman[133]	1997	Retrospective	Early CPAP vs intubation/ventilation or nasal CPAP or no nasal CPAP	127	Birth weight < 1,500 g	ND	ND	Early-CPAP group required less intubation/ventilation ($P < .02$).	30%
Lindner[136]	1999	Retrospective	Early CPAP (recruitment maneuver) vs intubation/ventilation and early CPAP	143	Birth weight < 1,000 g and gestational age ≥ 24 wk gestational age	4–6	Ventilator CPAP	Early-CPAP group had less CLD ($P < .05$), less intraventricular hemorrhage ($P < .01$), and fewer hospital days ($P < .05$).	46%
De Klerk[132]	2001	Retrospective	Early CPAP vs intubation/ventilation and nasal CPAP	116	Birth weight < 1,500 g	5	Bubble CPAP	Early-CPAP group had less necrotizing enterocolitis ($P = .02$), shorter stay ($P = .01$), less need for surfactant ($P < .001$), intubation/ventilation ($P < .001$), and less CLD at 28 d (no differences at 36 wk post-menstrual age).	8%
Jeena[14]	2002	Retrospective	Early CPAP vs intubation/ventilation and nasal CPAP	150	Birth weight < 1,900 g and < 34 wk gestational age	6	Infant Flow nasal CPAP	Early-CPAP group had lower mortality associated with congenital pneumonia ($P < .05$).	26%
Narendran[118]	2003	Retrospective	Early CPAP vs intubation/ventilation	171	Birth weight < 1,000 g	5	Bubble CPAP	Early CPAP group had fewer intubations and fewer days on ventilation ($P < .05$).	32%
Aly[140]	2004	Retrospective	Early CPAP vs intubation/ventilation and early CPAP	146	Birth weight < 1,500 g	5	Carden valve/bubble nasal CPAP	Early-CPAP group had less intubation/ventilation ($P = .02$), reduced need for surfactant ($P = .07$), and less CLD ($P = .03$).	19%
Sandri[127]	2004	Prospective	Early CPAP vs rescue nasal CPAP	230	Birth weight < 1,500 g and < 31 wk gestational age	4–6	Infant Flow nasal CPAP	No differences in outcomes	Early CPAP 23% Rescue CPAP group 22%
Finer[130]	2004	Prospective	Early CPAP vs no CPAP	104	< 28 wk gestational age	5–6	Neopuff	No differences in outcomes	Early CPAP 49% No CPAP 41%
Aly[129]	2005	Retrospective	Early CPAP vs intubation/ventilation	234	Birth weight < 1,500 g	5	Carden valve/bubble nasal CPAP	Early-CPAP (no failure) group had less need for surfactant ($P < .001$) than intubation/ventilation group. Early CPAP (with failure) had a higher incidence of necrotizing enterocolitis ($P = .02$) than intubation/ventilation group.	36%
Ammari[131]	2005	Retrospective	Early CPAP vs intubation/ventilation	261	Birth weight 500–1,250 g	5	Bubble CPAP	Early-CPAP (with failure) group had lower CLD ($P < .003$) and mortality ($P < .001$) than intubation/ventilation group. Early-CPAP (without failure) group had lower CLD ($P = .003$), intraventricular hemorrhage ($P = .02$), and mortality ($P < .001$) than early-CPAP (with failure) group.	24% (< 1,250 g) 50% (≤ 750 g)
Kugelman[138]	2007	Prospective	Early CPAP vs noninvasive IMV	84	< 35 wk gestational age	6	Ventilator CPAP	Noninvasive IMV group required less intubation/ventilation ($P = .06$) and had less CLD ($P < .03$).	49% failed early CPAP and 25% failed noninvasive IMV
Morley[139]	2008	Prospective	Early CPAP vs intubation/ventilation	607	Birth weight < 1,000 g and 25–28 wk gestational age	8	Bubble CPAP	Early CPAP had lower risk of death or CLD at 28 d ($P = .006$, no differences at 36 wk post-menstrual age). Early CPAP group had a higher incidence of pneumothorax ($P < .001$).	46%
Miksch[155]	2008	Retrospective	Early CPAP vs intubation/ventilation	243	Birth weight < 1,500 g	4–7	Bubble CPAP	Early-CPAP group had less intubation/ventilation ($P < .05$) and CLD ($P < .001$)	43% (< 1,500 g) 58% (< 1,000 g)
Birenbaum[135]	2009	Retrospective	Early CPAP vs intubation/ventilation and nasal CPAP	146	Birth weight 500–1,500 g	5	Bubble CPAP and/or Neopuff	Early CPAP group had less CLD ($P = .001$).	48%

CPAP = continuous positive airway pressure ND = no data/not mentioned F_{IO_2} = fraction of inspired oxygen RDS = respiratory distress syndrome CLD = chronic lung disease IMV = intermittent mandatory ventilation

Surfactant-replacement therapy has been perhaps the largest contributing factor in improving survival rate and reducing the severity in CLD in premature infants over the last 20 years. Infants born at < 30 weeks are at a greater risk of developing RDS, due to insufficient endogenous surfactant production, and these infants also are more likely to fail CPAP. Meta-analyses have demonstrated that prophylactic surfactant administration to infants at risk of developing RDS was associated with lower risk of air leak and mortality than was selective use of surfactant in infants with established RDS.[152] Currently, the conventional route for administering surfactant into infants' lungs is by instilling it down the ETT. In this case, infants typically require short-term ventilation following surfactant-replacement therapy, to allow some time for stabilization and lung absorption to occur. In recent years, the practice of intubation, administering surfactant replacement (10–15 min), and short-term ventilation (usually < 1 h), with immediate extubation to prophylactic CPAP has become a widely applied approach in supporting infants. This strategy has been adopted from a model of care commonly used in Scandinavia, and is frequently referred to as the "INSURE" (INtubate, SURfactant, Extubate) approach.[4,150]

One advantage of this prophylactic strategy is that all premature infants receive at least one dose of surfactant. This strategy also focuses on using a minimal duration of lung-protective mechanical ventilation. The duration of ventilation can range from 2 min or until the infant shows signs of improvement (ie, gas exchange or compliance) on the ventilator. The major disadvantage to this approach is that infants who may not necessarily need surfactant replacement are still subjected to the risks and complications associated with intubation and mechanical ventilation. A recent meta-analyses conducted by Stevens et al evaluated outcomes from 6 randomized controlled trials to compare early (prophylactic) surfactant administration with brief ventilation versus selective surfactant and continued mechanical ventilation for premature infants with or at risk of developing RDS.[153] Intubation and early surfactant administration followed by extubation to CPAP was associated with a lower incidence of mechanical ventilation (typical risk ratio 0.67, 95% CI 0.57–0.79), air leak syndromes (typical risk ratio 0.52, 95% CI 0.28–0.96), and CLD (typical risk ratio 0.51, 95% CI 0.26–0.99).

Rojas et al published the findings of a multicenter randomized controlled trial in premature infants (27–32 wk gestational age) assigned within the first hour of life to receive either early CPAP or intubation, very early surfactant, manual ventilation (approximately 2 min), and extubation to CPAP.[154] The group of infants supported initially with intubation, surfactant, brief manual ventilation, and extubation to CPAP had less need for intubation and mechanical ventilation ($P < .05$) and surfactant ($P < .003$), and less air leak and CLD ($P < .05$) than infants treated initially using early CPAP. In this study the addition of surfactant therapy following birth during a very brief period of standardized and controlled manual ventilation (using the Neopuff, Fisher & Paykel Healthcare, Irvine, California) and extubation to 6 cm H_2O CPAP proved to be effective in these infants.

Results from clinical research using the INSURE approach appear to show promise for reducing intubation and mechanical ventilation, as well as reducing the incidence of CLD in premature infants. The INSURE approach may be especially important for infants < 30 weeks, who have a higher likelihood for developing severe RDS requiring intubation. New approaches for administering surfactant during early CPAP, designed to eliminate the need for intubation and ventilation, may prove to be beneficial in supporting these infants. Table 3 shows clinical studies involving CPAP following extubation.

Based on the previous discussions, it becomes evident that not all infants can be supported using CPAP following delivery or even following extubation. Approximately 50% of infants with birth weight < 1,000 g and 25–40% of infants with birth weights between 1,000–1500 g fail early CPAP and require intubation and mechanical ventilation.[131,139,155] Approximately 25–38% of infants with birth weights 1,000–1500 g fail CPAP following surfactant administration, resulting in re-intubation and mechanical ventilation.[74,154,156] A number of predictors and factors have been helpful in identifying reasons why infants fail CPAP. Common predictors for infants failing early CPAP include lower birth weight (≤ 750 g) and gestational age (< 26 wk), higher severity of RDS (increased alveolar-arterial oxygen difference), and need for resuscitation at birth.[131] Ammari et al evaluated differences in outcomes between infants treated successfully with early CPAP and in infants who failed CPAP.[131] The CPAP-failure group had higher mortality ($P < .001$), rate of pneumothorax ($P < .003$), incidence of CLD ($P < .001$), and intraventricular hemorrhage ($P = .02$) than did the CPAP-success group.

Stefanescu et al evaluated reasons for infants failing CPAP following surfactant administration, which resulted in re-intubation.[74] In a combined cohort of 116 premature infants, 58% of infants who failed extubation (or required intubation) did so because of apnea/bradycardia, 16% from refractory hypoxemia ($F_{IO_2} > 0.5$, CPAP > 8 cm H_2O), 15% from ventilation failure ($P_{aCO_2} > 65$ mm Hg, pH < 7.25), 3% from surgery, and 8% from other reasons.

Aside from the recurrent apnea, extremely-low-birth-weight premature infants are generally weaker and lack the brown fat stores that are required to sustain periods of high metabolic demand related to increased WOB. Furthermore, the lungs of these extremely-low-birth-weight infants are stiffer, smaller, and lack mature surfactant. Jobe et al reported in premature lambs exhibiting greater respiratory distress and failure (indicated by $P_{aCO_2} > 100$ mm Hg)

Table 3. Clinical Studies Evaluating CPAP Following Extubation

First Author	Year	Design	Respiratory Strategy Following Extubation	*n*	Sample Patients	CPAP Level (cm H_2O)	CPAP Technique	Summary of Outcomes	Re-intubation (%)
Engelke[144]	1982	Prospective	CPAP vs oxygen hood	18	Birth weight > 1,000 g	6	ND	Infants supported with CPAP had lower alveolar-arterial oxygen difference ($P < .05$), P_{aCO_2} ($P < .01$), and respiratory rate at 24 h ($P < .01$).	CPAP 0% Oxygen hood 22%
Higgins[145]	1991	Prospective	CPAP vs oxygen hood (crossover to CPAP for failure)	58	Birth weight < 1,000 g	4–6	ND	66% of infants were successfully extubated to CPAP, compared with 40% of oxygen hood group ($P < .001$).	ND
Chan[149]	1993	Prospective	CPAP vs oxygen hood	60	Birth weight < 1,800 g	3	ND	There were no differences in any outcomes between the study groups.	ND
Annibale[141]	1994	Prospective	CPAP vs CPAP (short-term, 6 h) vs oxygen hood	124	Birth weight 600–1,500 g	6	Ventilator CPAP	There were no differences in any outcomes between the study groups.	CPAP 35% CPAP (short-term) 33% Oxygen hood 31%
So[125]	1995	Prospective	CPAP vs oxygen hood	50	< 34 wk gestational age, < 1,500 g	5	Bubble CPAP	84% of infants were successfully extubated to CPAP, compared with 48% infants in the head box group ($P = .02$).	CPAP 16% Oxygen hood 52%
Davis[142]	1998	Prospective	CPAP vs oxygen hood	92	Birth weight 600–1250 g	7	Ventilator CPAP	Infants supported with CPAP reached successful extubation criteria (apnea, oxygen requirement > 15%, and respiratory acidosis) earlier ($P = .01$).	CPAP 34% Oxygen hood 31%
Robertson[147]	1998	Prospective	CPAP vs rescue CPAP	58	Birth weight < 1,000 g	4–6	Infant Flow CPAP	There were no differences in any outcomes between the study groups.	CPAP 21% Rescue CPAP 24%
Verder[156]	1999	Prospective	CPAP (following early surfactant) vs CPAP (following later surfactant)	30	< 30 wk gestational age	6	Benveniste gas-jet valve	CPAP (following early surfactant) had less ventilation and/or death at < 7 d ($P = .001$) and before discharge ($P = .004$). CPAP (following early surfactant) had less patent ductus arteriosus ($P < .02$) and less need for ventilation at discharge ($P = .005$).	CPAP (following early surfactant) 25% CPAP (following later surfactant) 68%
Dimitriou[143]	2000	Prospective	CPAP vs oxygen hood	150	< 34 wk gestational age	ND	ND	There were no differences in any outcomes between the study groups.	CPAP 15% Oxygen hood 9%
Peake[146]	2005	Prospective	CPAP vs oxygen hood	97	< 32 wk gestational age	4–6	Infant Flow CPAP	There were no differences in any outcomes between the study groups.	CPAP 51% Oxygen hood 48%
Dani[148]	2004	Prospective	CPAP vs intubation/ventilation (CPAP 2 h later)	27	< 30 wk gestational age	4–7	Infant Flow CPAP	Nasal CPAP group had less need for ventilation at 7 d ($P = .03$), shorter duration of ventilation ($P < .001$), were less likely to require a second dose of surfactant ($P < .006$), and had shorter stay in the intensive care unit ($P = .02$).	CPAP 0% Endotracheal intubation and mechanical ventilation (with CPAP 2 h later) 22%
Rojas[154]	2009	Prospective	CPAP (following surfactant and very brief intubation/ventilation) vs early CPAP	278	27–32 wk gestational age	6	Bubble CPAP	CPAP (following surfactant and very brief intubation/ventilation) and extubation to CPAP had less need for intubation/ventilation ($P < .05$) and surfactant ($P < .003$), and less air leak and chronic lung disease ($P < .05$)	CPAP (following surfactant very brief endotracheal intubation and mechanical ventilation) 26% Early nasal CPAP 39%

CPAP = continuous positive airway pressure ND = no data/not mentioned

during CPAP treatment generally had lower levels of surfactant (saturated phosphatidylcholine level of 1.9 μmol/kg, approximately 3% the levels observed in term lambs) and less endogenous surfactant secretion than did animals that were able to be supported by CPAP.[53]

The CPAP failure rate is high, and clinicians therefore have begun using traditional invasive ventilation strategies (mechanical ventilation, high-frequency oscillatory ventilation, SiPAP) noninvasively, with little evidence base to support their use. These approaches elucidate the need for new intermediary noninvasive devices that provide a higher level of support to reduce WOB, stimulate the infant to breath, and improve gas exchange in order to optimize the care of infants failing CPAP.

Clinical Management

The clinical management of infants supported by CPAP is based more on anecdotal experience, opinion, and conventional wisdom than on actual scientific evidence, and these practices vary greatly from one institution to another. There is no consensus regarding the proper initial CPAP level, weaning strategies, or appropriate timing for implementation and weaning during the course of lung disease. According to the American Association for Respiratory Care's clinical practice guidelines: CPAP is indicated by the presence of

> increased WOB, as implied by an increase in respiratory rate of > 30% of normal, substernal and suprasternal retractions, grunting, and nasal flaring, the presence of pale or cyanotic skin color, agitation . . . the inability to maintain a P_{aO_2} > 50 mm Hg with F_{IO_2} of ≤ 0.60 . . . a P_{aCO_2} level of 50 mm Hg and a pH ≥ 7.25, and the presence of poorly expanded and/or infiltrated lung fields on chest radiograph.[17]

In a recent survey of delivery room practices in the United States, the initial CPAP level used was 5 cm H_2O in 191 programs (56%), 4 cm H_2O in 49 programs (14%), 6 cm H_2O in 47 programs (14%), and 7 cm H_2O in 2 programs (0.5%).[157] However, optimal CPAP levels up to 12 cm H_2O may be necessary to optimize lung volumes in infants with extremely non-compliant lungs.[39] Higher CPAP levels may be needed in order to recruit lungs with low compliances; however, values exceeding 8–10 cm H_2O are more likely to result in oral leakage, and CPAP levels exceeding 10–12 cm H_2O have been associated with greater risk of gastric insufflation.[64]

The CPAP level requirements are likely to fluctuate throughout the course of treatment. The optimal level of CPAP is one that results in adequate lung inflation and gas exchange without overdistending the lung parenchyma. Determining the optimal level of CPAP is a technically challenging process, because few objective measurements exist to determine adequacy of lung recruitment using inherently leaky nasal prongs. Blood gases and chest radiographs can be helpful in determining patient response to CPAP; however, frequent radiographs and blood gases can also be detrimental to neonatal patients. Transcutaneous monitoring of CO_2 and pulse oximetry offer reliable correlates for determining gas exchange in patients supported by CPAP. Permissive hypercapnia is becoming a widely used method in infants supported by CPAP, where it is acceptable to allow the pH level to fall to 7.25 and the P_{aCO_2} to rise to 65 mm Hg before initiating intubation and mechanical ventilation.[158] This practice alone could impact outcomes by further reducing the need for intubation and ventilation. No absolute defined limits exist for determining safe pH and P_{aCO_2} levels during CPAP; however, extreme hypercapnia increases the risk of developing intraventricular hemorrhage in small infants, and hypocapnea can cause periventricular leukomalacia.[159]

Following lung recruitment, the F_{IO_2} should be weaned immediately upon confirmation of acceptable blood gas values or pulse-oximetry measurements, to avoid potential complications caused by hyperoxemia.[160] If a patient still remains on a higher F_{IO_2} (> 0.5) with marginal oxygenation, following implementation of CPAP, then the CPAP level could be lower than the closing pressure of the lungs, and alveolar recruitment is not being achieved. Also, infants who continue to have refractory oxygenation should be evaluated for patent ductus arteriosus. A rise in P_{aCO_2} or fall in P_{aO_2} after increasing the CPAP pressure may indicate improving compliance, which can result in pulmonary hyperinflation and increased alveolar dead space.[72] Apnea is also a frequent concern in patients supported by CPAP; however, a loading dose of 20 mg/kg of caffeine citrate followed by a daily maintenance dose of 5 mg/kg (up to 10 mg/kg) can reduce the incidence of apnea.[161]

Proper airway management is perhaps the single most important aspect of improving outcomes and reducing complications in infants receiving CPAP. This becomes particularly important because infants are being supported for longer periods of time during CPAP. A number of resources are available that provide useful and detailed information related to the bedside airway management of such infants.[72,59,162] Briefly, clinicians caring for infants receiving CPAP are mindful of selecting the proper prong size that fills the entire nare without blanching the external nares but is not too small; proper size avoids increasing the imposed WOB, prong displacement, and excessive leaks. Often, infants are suctioned and the nasal airway is evaluated for skin breakdown. The fixation technique is also an important aspect. Various manufacturers have specific guidelines for selecting the proper hat and prong size. The hat should be tight and the straps connecting the nasal

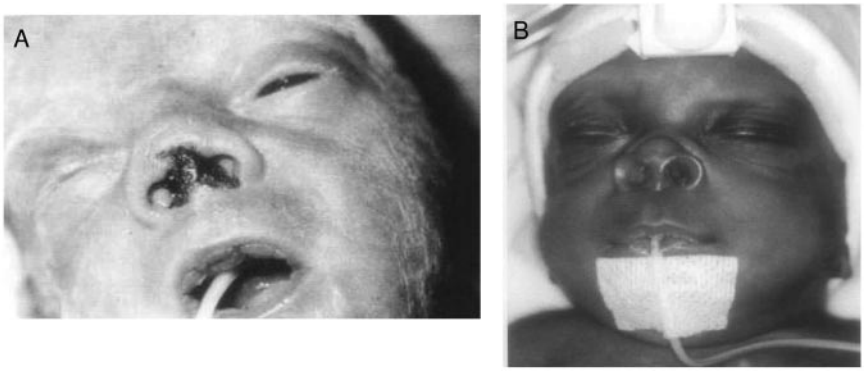

Fig. 11. Nasal injuries from continuous positive airway pressure (CPAP). A: Columnella necrosis from short-term CPAP. B: Circular distortion of nares from long-term CPAP use. (From Reference 167, with permission.)

interface should be adjusted to apply only minimal tension on the infant's nasal anatomy. The lack of stabilization and, hence, excessive movement of the prongs could result in nasal injury, interface displacement, and loss of system pressure.[72]

Complications

The most frequent complications that are reported with CPAP include equipment failures, nasal airway injury, and air leak. Obstruction of nasal prongs from mucus plugging or tips pressed against the nasal mucosa can lead to low end-expiratory lung volume and consequential deterioration and increased WOB.[162,163] Local irritation and trauma[164,165] to the nasal septum may occur due to misalignment or improper fixation of nasal prongs.[166] Breakdown and erosion low on the septum at the base of the philtrum can occur when using nasal masks, and columnella necrosis can occur after only short periods of receiving CPAP (Fig. 11A).[167] Nasal snubbing and circumferential distortion (widening) of the nares can be caused by nasal prongs, especially if CPAP is being used for more than just a few days (see Fig. 11B). Inadequate humidification can lead to nasal mucosal damage.[168] Skin irritation of the head and neck from improperly secured bonnets or CPAP head harnesses can also occur. Equipment failure and dysfunction should always be considered as a potential source for complicating an infant's condition when providing CPAP.[72]

The noninvasive application of CPAP is a form of positive-pressure ventilation and, therefore, some of the same complications that arise during mechanical ventilation can also occur during CPAP. Air leak, although not reported frequently, is still a concern, especially when an inappropriately high CPAP level is used. Pneumothorax,[163,165,169] pulmonary interstitial emphysema, pneumomediastinum, pneumatocele,[170-174] and vascular air embolism[175] have been described in infants receiving CPAP. One study compared cardiac output and stroke volume measurements in spontaneously breathing premature infants to infants receiving CPAP and there no were no detectable differences in these hemodynamic values.[176] CPAP has also been associated with increased intracranial pressures[177] and decreased urine output and glomerular filtration rate.[178] Bowel distention is often a mild complication noted with CPAP, which may occur when an infant swallows air, and can be relieved using an orogastric tube.[179]

Summary

CPAP is an attractive option for supporting infants with respiratory distress, because it preserves spontaneous breathing, doesn't require an ETT, and has been shown to be less injurious and may result in less CLD than intubation and mechanical ventilation. However, there have been few prospective randomized controlled trials evaluating outcomes in infants receiving CPAP, compared to infants managed using current lung-protective mechanical ventilation strategies. Furthermore, there is no consensus about whether all premature infants supported by CPAP should be done so directly following delivery or following a prophylactic dose of endogenous surfactant and brief ventilation. Premature infants < 30 weeks and $< 1{,}000$ g, are more likely to fail CPAP and may benefit from surfactant and brief ventilation followed by CPAP, whereas older and larger infants appear to be managed effectively using CPAP as the initial and primary method for support. Despite the successes, little is known about how best to manage patients using CPAP. It is also unclear whether different strategies or devices used to maintain CPAP play a role in improving outcomes in infants. Nasal CPAP technology has evolved over the last 10 years, and bench and clinical research has evaluated differences in physiologic effects related to these new devices, but there have been no clinical trials demonstrating major differences in outcomes when comparing these devices in the clinical setting. Ultimately, the clinicians' abilities to perceive changes in the

pathophysiologic conditions of infants receiving CPAP and the quality of airway care provided are likely to be the most influential factors in determining successful outcomes in patients.

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