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Clin Perinatol 33 (2006) 803–830

CLINICS IN
PERINATOLOGY

Hypoxic Respiratory Failure in the Late Preterm Infant

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They have been aptly called the great imposters; late preterm infants (also called near-term) often are passed off as mature infants, but manifest signs of physiologic immaturity or delayed transition in the neonatal period [1]. Births between 34 and 37 weeks gestation (referred to herein as late preterm births) account for a significant proportion of preterm births in North America and elsewhere. Several studies have documented the high incidence of respiratory distress and neonatal ICU (NICU) admissions in this population [2–4]. These infants have a higher incidence of transient tachypnea of the newborn (TTNB), respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), and respiratory failure than term infants [3]. Data about respiratory failure and outcomes in near-term infants are hard to obtain because of the lack of large databases such as those available for preterm infants. It is estimated, however, that 17,000 infants greater than or equal to 34 weeks are admitted to NICUs each year in the United States alone, and these represent up to 33% of all NICU admissions [5]. Nearly 50% of infants born at 34 weeks gestation require intensive care; this number drops to 15% at 35 weeks and 8% at 36 weeks gestation. In addition to respiratory distress, these infants often have other neonatal complications including hypoglycemia, hyperbilirubinemia, feeding difficulties, and difficulty in maintaining body temperature. Long-term morbidity information is even harder to gather; an estimated 9% of normal birth weight infants with respiratory failure die in the neonatal period [5]. Factors associated with high morbidity and mortality include delivery by cesarean section, presence of maternal complications, male gender, and intrauterine growth retardation.

In obstetric and pediatric practice, late preterm infants often are considered functionally mature and are managed based on protocols developed for

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doi:10.1016/j.clp.2006.09.006 *perinatology.theclinics.com*

full-term infants. The late preterm infant has been excluded from randomized controlled trials (RCTs) that focus on respiratory diseases of the more vulnerable very preterm infant (eg, trials of surfactant replacement for the treatment of RDS and antenatal steroids for the prevention of RDS). Instead they have been included in large multi-center, RCTs designed to assess the efficacy and safety of newer ventilatory strategies and rescue therapies in neonates with hypoxemic respiratory failure (HRF) born at 34 weeks gestation or more. Unlike studies in the preterm population, studies in term and the late preterm populations uniformly fail to either stratify by gestational age or use gestational age as a major confounder when analyzing outcomes. Therefore, the evidence that is used to treat HRF in the late preterm is extrapolated from studies where most infants enrolled are either term or postdates, and the mean gestational age is 39 plus or minus 2 weeks [6–10]. Based on data from the Extracorporeal Life Support Organization (ELSO) Neonatal Registry, gestational age is a major determinant of survival. Not only is prematurity associated with decreased survival in infants born with congenital diaphragmatic hernia but early term birth (37 to $39^{6/7}$ weeks) results in a higher mortality than late term birth (40 to $42^{6/7}$ weeks) [11]. Similar information is not available for other respiratory diagnoses, but overall survival of the late preterm population with neonatal respiratory failure was 96% compared with 98% at term in a large cohort study done in Italy in the mid 1990s [12].

Delayed respiratory transition in late preterm infants

The last few weeks of gestation are critical for fetal development and maturation, gradually preparing the fetus for a safe landing. Biochemical and hormonal changes that accompany spontaneous labor and vaginal delivery also play an important role in this transition. For effective gas exchange to occur, alveolar spaces must be cleared of excess fluid and ventilated, and pulmonary blood flow increased to match ventilation with perfusion. Failure of either of these events can jeopardize neonatal transition and cause the infant to develop respiratory distress. Understanding of the mechanisms(s) by which fetal lungs are able to clear themselves of excessive fluid at birth remains far from complete. It is clear though, that traditional explanations that relied on Starling forces and vaginal squeeze can account for only a fraction of the fluid absorbed [13–18]. Amiloride-sensitive sodium transport by lung epithelia through epithelial sodium channels (ENaC) has emerged as a key event in the transepithelial movement of alveolar fluid [19–27], and this appears to be a two-step process. The first step is passive movement of Na^+ from lumen across the apical membrane into the cell through Na^+-permeable ion channels. The second step is active extrusion of Na^+ from the cell across the basolateral membrane into the serosal space. The lung epithelium is believed to switch from a predominantly chloride-

secreting membrane at birth to a predominantly Na^+-absorbing membrane after birth. These changes also have been correlated with an increased production of the mRNA for amiloride-sensitive epithelial Na^+ channels (ENaC) in the developing lung [23]. Disruption of this process has been implicated in several disease states including TTNB [28] and RDS [29]. It is known now that the experience of vaginal delivery greatly enhances respiratory performance, and this effect is greater than that achieved by simple reduction of lung liquid volume to half in fetuses delivered without enduring labor. Removal of lung fluid starts before birth and continues postnatally with fluid being carried away by several possible pathways including pulmonary lymphatics [30,31], blood vessels [32], upper airway, mediastinum [33], and pleural space [33]. In later life, pulmonary edema can result either from excessive movement of water and solute across the alveolar capillary membrane, or from failure of reabsorption of lung fluid [34,35].

Respiratory morbidity in late preterm neonates born by cesarean section without trial of labor

A significant number of late preterm neonates are delivered by cesarean section, and this number has been steadily increasing in North America. Overall, cesarean births rose a seventh year in a row in 2003 to a record 27.6% of all deliveries (National Vital Statistics Report, 2004), [36–40]. This rate is 33% higher than the rate seen in 1996 and is accompanied by a 16% drop in women attempting vaginal birth after a previous cesarean section in 2003 over the previous year (National Vital Statistics Report, 2004). Among many reasons cited for this increase are more older women giving birth, a rise in multiple gestations, and physicians' concerns about risks of vaginal birth [41]; predictions are that continued increases are inevitable. Rates of cesarean section are considerably higher in some other parts of the world, especially in Latin America [42–43]. Although indications for the high rate of operative deliveries can vary by region and by maternal choice, up to 50% of these procedures may be performed because of a previous cesarean section [36,44].

A higher occurrence of respiratory morbidity in late preterm and term infants delivered by elective cesarean section has been observed by many investigators [45–53]. These infants have a higher incidence of TTNB [45–52,54], RDS resulting from iatrogenic prematurity [45–47,55,56], and severe PPHN or HRF [49,50]. Some of these reports also show higher rates of NICU admissions, mechanical ventilation, oxygen therapy, extracorporeal life support (ECMO), and death [49,50]. Madar and colleagues [55] showed that infants born by ECS at 37 to 38 weeks are 120 times more likely to receive ventilatory support for RDS than those born at 39 to 41 weeks. In contrast, a large population-based longitudinal study of 6138 women in Nova Scotia comparing trial of labor to repeat elective cesarean section failed to show an increase in

respiratory morbidity in infants born without enduring labor [44]. No neonatal data, however, were presented in this report, and it is not clear if the overall occurrence of respiratory morbidity in the two groups studied was higher than that of infants delivered by normal spontaneous vaginal delivery [44].

It is also important to remember that the bulk of deliveries in the United States occur at community hospitals (3024 community hospitals and 241 academic medical centers that deliver babies), and many serve rural populations. Multiple factors contribute to less rigorous dating and timing of deliveries in these settings. Once born, late preterm infants often are cared for in term nurseries by pediatricians. Transitional care in these infants, however, often requires a higher level of monitoring and support [57].

Why do elective cesarean deliveries carry a higher risk for the neonate? Because elective cesarean section is commonly performed between 37 and 40 weeks gestation [58], it was believed that much respiratory morbidity in newborns delivered by elective cesarean section is secondary to iatrogenic prematurity. Indeed, studies evaluating large series of patients have shown a higher rate of prematurity [45–47] and surfactant deficiency [55] in these patients. Morrison and colleagues [51] showed that respiratory morbidity in elective cesarean section is related inversely to gestational age at the time of surgery: 73.8/1000 in the 37 th week, 42.3/1000 in the 38 th week, and 17.8/1000 in the 39 th week of gestation. To minimize the occurrence of iatrogenic RDS, fetal lung maturity testing was recommended initially before elective cesarean section, but this is seldom done given the risks associated with amniocentesis. Delaying elective cesarean section to 38 to 40 weeks has been shown to decrease the risk of respiratory distress, but this carries the risk of the patient going into spontaneous labor. Further, it is clear that in addition to RDS, infants delivered by elective cesarean section are at higher risk of developing TTNB and PPHN unrelated to their gestational age at the time of delivery. Although most of these neonates develop transient respiratory distress and recover without any long-term consequences, a significant number progress to severe respiratory failure [50]. These infants not only require prolonged hospitalization, but also are at increased risk for chronic lung disease and death [50]. In addition, there is a higher incidence of respiratory depression at birth (low Apgar scores) [54], thought to be related to fluid-clogged lungs, making the transition to air breathing more difficult.

In an effort to reduce the occurrence of iatrogenic prematurity associated with elective cesarean section deliveries, the American College of Obstetrics and Gynecology [59] recommends scheduling elective cesarean section at 39 weeks or later on the basis of menstrual dates, or waiting for the onset of spontaneous labor. It also lays down the criteria for establishing fetal maturity before elective cesarean section. As alluded to earlier, however, the safety of this approach in mothers with previous cesarean section deliveries has not been established in rigorous trials. Some population-based studies

[60] point to an increased risk of uterine rupture and perinatal death in mothers with previous cesarean section who went into spontaneous labor after 39 weeks. Such findings, and factors related to the convenience of scheduled elective cesarean section deliveries for both families and providers, will continue to influence the timing of elective cesarean section.

Severe hypoxic respiratory failure in late preterm infants

The general impression among clinicians is that TTNB is a benign self-limited illness that requires minimal intervention. Although respiratory distress from TTNB and other causes is seen frequently in infants delivered by elective cesarean section, it is not known how many of these infants become seriously ill and require clinical intervention. It is not clear if the risk-to-benefit ratio of an intervention that is designed to reduce respiratory morbidity in infants delivered by ECS will justify its clinical application in a large number of mothers. One approach would be to evaluate the true occurrence of severe hypoxic respiratory failure in this population [61]. Heritage and Cunningham [49] and Keszler and colleagues [50] reported severe respiratory morbidity and resulting mortality in infants born by elective cesarean section who developed pulmonary hypertension, hence the term malignant transient tachypnea of newborn (TTN). A significant number of these infants required ECMO [50]. The etiology of pulmonary hypertension and HRF in late preterm is not entirely clear. Many of these infants are asymptomatic immediately after birth or have mild respiratory distress, low oxygen requirements, and radiographic findings suggestive of retained lung fluid or mild RDS. In a subset of infants, however, there is a gradual increase in oxygen requirements and subsequent evidence of PPHN. Oxygen often is provided by oxyhoods. There are studies, especially in the adult anesthesia literature, that document a high incidence of alveolar collapse because of oxygen absorption and denitrogenation (nitrogen washout) [62,63]. Rothen and colleagues [62,63] have shown that in the postoperative period, atelectasis is twice more common in patients ventilated with 100% oxygen as compared with 30% oxygen. Detailed study of late preterm infants who required ECMO is warranted to better understand the pathophysiology of HRF in this population and the influence of confounding variables.

The authors recently reviewed data from the ELSO Neonatal Registry to study the demographic characteristics, ECMO course, morbidity, and mortality in late preterm infants. Infants with congenital anomalies including congenital diaphragmatic hernia were excluded. From 1989 to 2006, 15,590 neonates treated with ECMO were registered with ELSO. Of these, 2258 (14.5%) neonates were late preterm. Their demographic characteristics are shown in Table 1. The mean gestational age and birth weight of late preterm infants were 35.3 plus or minus 0.9 weeks and 2.8 plus or minus 0.51 kg respectively. More late preterm infants treated with ECMO were

Table 1
Demographic characteristics of the late preterm and term extracorporeal membrane oxygenation population

	Late preterm (N = 2062)	Term (N = 12,336)	*P*
Birth weight	2.82 ± 0.50 kg	3.42 ± 0.56 kg	<.0001
Gestation	35.4 ± 0.8 wks	39.7 ± 1.5 wks	<.0001
Male	66%	57%	<.0001
Median apgar 1	6	5	<.0001
Median apgar 5	8	7	<.0001

Data expressed as mean ± SD or percentage.

non-Hispanic whites and were delivered by elective cesarean section. The primary etiology of hypoxic respiratory failure in late preterm infants was RDS or sepsis as compared with term infants who were more likely to have aspiration syndromes. Pulmonary hypertension was reported with equal frequency in both groups. Data related to the ECMO course are summarized in Table 2. Late preterm infants were older at cannulation and had a longer duration of ECMO support. Table 3 compares the major complications reported in late preterm and term infants. Late preterm infants were more likely to have intraventricular hemorrhage and other neurologic complications than term infants. They were also more likely to die on ECMO or have ECMO support discontinued before lung recovery. The overall survival rate was 74% for late preterm infants as compared with 87% for term infants ($P < .0001$). Survival in the late preterm neonatal ECMO population fell from 81.5% in 1989 to 65.2% in 2005 (Fig. 1). Gestational age continued to be an independent risk factor for mortality in neonates treated with ECMO after correction for race, diagnosis, mode of delivery, and 5-minute Apgar score.

Table 2
Extracorporeal membrane oxygenation course in late preterm and term infants

	Late preterm (N = 2062)	Term (N = 12,336)	*P*
Age on ECMO	2.6 ± 3.3 days	2.2 ± 2.8 days	<.0001
Hours on ECMO	145 ± 102 hrs	136 ± 86 hrs	<.0001
Lung support (%)	99	99	NS
Discontinuation or death on ECMO	28.2%	15.5%	<.0001
Survival	74%	87%	<.0001

Late preterm infants were older at cannulation, had a longer duration of ECMO support, and had a significantly lower survival rate when compared to term infants. Data expressed as mean ± SD or percentage.

Abbreviations: ECMO, extracorporeal membrane oxygenation; NS, not significant; SD, standard deviation.

Table 3
Extracorporeal membrane oxygenation complication rates in late preterm and term infants

Complication	Late preterm (%)	Term (%)	RR	95% CI
Hemorrhagic	6.4	8.4	0.76	0.68–0.84
Mechanical	1.4	1.5	0.94	0.87–1.00
Metabolic	8.8	7.1	1.25	1.14–1.37
Neurologic	12.4	8.2	1.51	1.40–1.63
IVH	4.4	1.9	2.33	2.02–2.69
Other	8.0	6.3	1.27	1.15–1.39
Hemofiltration/dialysis	7.3	5.6	1.31	1.18–1.45
Culture-proven infection	2.6	2.4	1.11	0.94–1.32
Major cardiovascular	4.1	3.7	1.06	0.95–1.18
PDA	1.8	1.9	0.93	0.76–1.14
Other	4.1	3.7	1.12	0.98–1.21
Pulmonary hemorrhage	1.5	1.4	1.12	0.90–1.40

Late preterm infants were more likely to have intraventricular hemorrhage and other neurologic complications than term infants.

Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosis; RR, relative risk.

Management strategies for late preterm infants with hypoxic respiratory failure

Approximately 30,000 late preterm and term infants in the United States require mechanical ventilation each year secondary to neonatal respiratory failure [5]. Eighty five percent of these infants will fail to respond to conventional ventilation with high fractional oxygen concentrations and will develop neonatal HRF, which will require adjunctive therapies [3]. These infants have a higher mortality than preterm infants with acute respiratory failure [64]. Respiratory insufficiency occurs in late preterm and term infants as a complication of perinatal asphyxia, elective cesarean birth, perinatal aspiration syndromes, pneumonia, sepsis, RDS, pulmonary hypoplasia, and

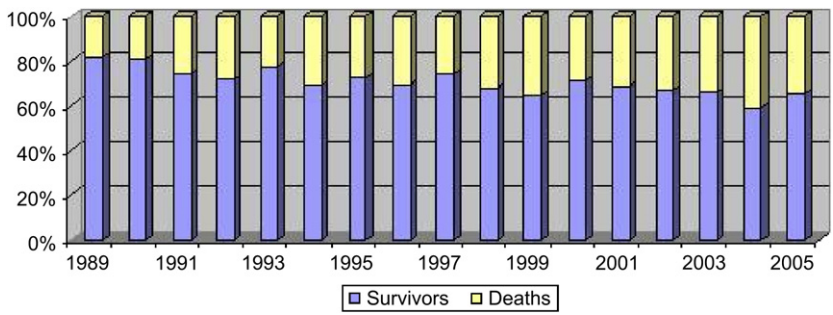

Fig. 1. Change in survival of late preterm infants treated with extracorporeal membrane oxygenation (ECMO) since 1989. Survival in this population fell from 81.5% in 1989 to 65.2% in 2005 in spite of improvements in ECMO.

other congenital anomalies of the lung. Maternal ingestion of nonsteroidal anti-inflammatory drugs [65] and late trimester use of selective serotonin reuptake inhibitors [66] have also been implicated as possible causes of some cases of PPHN. The progression from respiratory insufficiency to neonatal HRF is accompanied by:

- Pulmonary artery hypertension with right-to-left shunting via fetal pathways
- Surfactant dysfunction with associated alveolar collapse
- Ventilator-induced lung injury

Newer techniques and adjuvant treatments have improved survival rates in this population by addressing the pathophysiology of HRF. These include administration of exogenous surfactant, iNO, high-frequency ventilation and ECMO. Liquid ventilation also has shown some promise in this regard [67].

Supportive care

Infants who have HRF require attention to detail. Continuous monitoring of oxygenation, blood pressure, and perfusion is critical. The oxygenation index ($OI = Paw \times FiO_2 \times 100/Pao_2$) should be calculated for each arterial blood gas sample. The highest OI during the first 24 hours of life recently was found to be useful in predicting the outcome of HRF with results comparable to the SNAP II score [68]. Infants with PPHN frequently have right-to-left shunting across the patent ductus arteriosus. This can be demonstrated by pre- and postductal arterial blood gas sampling or placement of oximeter probes. Although it is a useful indicator of PPHN when present, a ductal shunt is frequently absent in late preterm and term infants who have PPHN.

Management of fluids and electrolytes is important. Normal values for glucose and ionized calcium should be maintained, because hypoglycemia and hypocalcemia tend to worsen PPHN. An adequate circulating blood volume is crucial to maintain right ventricular filling and cardiac output. Excessive volume administration, however, can lead to pulmonary edema and cardiac decompensation. Colloid infusions have not been shown to be superior to crystalloid solutions in restoring circulatory volume in hypotensive infants [69], children, and adults [14] and have been shown to worsen oxygenation in adult patients with acute respiratory distress syndrome (ARDS) [70] and renal function in neonatal ECMO patients [71]. Colloid infusions and blood products should be reserved for specific indications (eg, the correction of abnormal coagulation studies). The platelet count frequently is depressed in infants who have HRF regardless of the underlying disease; however, transfusion of platelets may result in increased pulmonary vasospasm or deposition of platelet thrombi in the pulmonary

microcirculation [72]. Polycythemia can result in hyperviscosity syndrome and may cause or aggravate PPHN and anemia because acute blood loss can result in right-to-left shunting, hypotension, and systemic hypoperfusion. Both conditions require immediate treatment. Inotropic support with dopamine and dobutamine, alone or in combination, may be helpful in maintaining adequate cardiac output and systemic blood pressure [73]. Epinephrine and norepinephrine also have been used in this setting [74]. Infants who have vasopressor-resistant hypotension may benefit from steroid replacement [75].

A chest radiograph is useful for assessing underlying parenchymal lung disease, and it can exclude anomalies such as congenital diaphragmatic hernia. In infants who have idiopathic PPHN, the lung fields typically appear clear, with decreased vascular markings and a normal heart size. A two-dimensional echocardiogram is generally necessary to exclude cyanotic congenital heart disease. Defining the anatomy of the pulmonary veins can be extremely difficult if extrapulmonary right-to-left shunting of blood is present. Likewise, the diagnosis of coarctation of the aorta may be difficult in infants whose ductus arteriosus is widely patent. If the echocardiogram is not definitive, cardiac catheterization may be necessary to exclude these and other cardiac lesions. Color flow Doppler imaging can be used to determine if right-to-left shunting of blood across the ductus arteriosus, foramen ovale, or both is present. The peak velocity of the regurgitant flow across the tricuspid valve can be used to estimate right ventricular systolic pressure. The peak velocity of left-to-right or right-to-left flow in the ductus arteriosus can be used to estimate pulmonary artery pressure. Other echocardiographic findings suggestive of PPHN include right atrial dilation, right ventricular dilation, bowing of the interatrial or interventricular septum to the left, and flattening of the interventricular septum. The echocardiogram also can be helpful for assessing ventricular performance. Right ventricular dysfunction can cause right-to-left atrial shunting across the foramen ovale and decrease pulmonary blood flow in the absence of PPHN. Severe left ventricular dysfunction leads to right-to-left shunting at the ductal level, elevates left atrial pressure, and results in pulmonary edema and systemic hypoperfusion, acidosis, and multi-organ system dysfunction. Treatment with pulmonary vasodilators in this circumstance can result in cardiovascular collapse [76]. Cranial ultrasonography should be performed if the infant is being considered for extracorporeal life support. This is especially true in the late preterm infant who is at increased risk of intracranial hemorrhage on ECMO [77,78].

When caring for infants, the use of a protocol to minimize handling is imperative. Sedation and analgesia with opiates is often necessary to decrease sympathetic tone during stressful interventions and blunt the pulmonary vascular response to noxious stimuli. Fentanyl is the most frequently used opiate. Acute muscle rigidity, or chest wall syndrome, may occur following rapid infusion. Prolonged exposure leads to accumulation in fat and delays

weaning. Tolerance develops rapidly, and significant withdrawal symptoms may develop if infusions are used for more than 5 days. Fentanyl has minimal effect on the cardiovascular system; however, the addition of benzodiazepines or other sedatives may decrease cardiac output and blood pressure [79]. The use of paralytic agents is controversial and reserved for the infant who cannot be treated with sedatives alone. The use of muscle relaxants may promote atelectasis of dependent lung regions and ventilation perfusion ratio (V/Q) mismatch. A review of 385 newborns with PPHN by Walsh-Sukys and colleagues suggests that paralysis may be associated with an increased risk of death [80].

Mechanical ventilation

Mechanical ventilation with high inspired oxygen concentration is the main support modality for the treatment of neonates with HRF. However, it has become apparent that mechanical ventilation can lead to numerous serious complications, including initiation or exacerbation of underlying lung injury. Mechanical ventilation with high fractions of inspired oxygen and high inspiratory pressures has been implicated in the pathogenesis of bronchopulmonary dysplasia [81]. In the late preterm and term infant, the pathophysiology of ventilation-induced lung injury is more akin to that of adult respiratory distress syndrome and involves factors such as complement, oxygen free radicals, proteases, endotoxin, eicosanoids, platelet activating factor, cytokines, growth factors and kallikreins [82–86]. Research over the past two decades has focused primarily on the mechanical forces producing ventilator-induced lung injury. Despite intense research and numerous innovations in ventilatory therapy aimed at minimizing such injury, the morbidity and mortality of acute respiratory failure remains high, and ventilator-induced lung injury remains a significant problem for the critically ill neonate [87]. In newborns developing HRF, only a small percentage goes on to die of respiratory failure. Rather, lung injury results in the development of a systemic inflammatory response that culminates in multi-organ dysfunction syndrome (MODS) and death [81].

One possible explanation for this observation is that mechanical ventilation initiates or potentiates an inflammatory response in the lung, which in turn results in a vicious cycle of inflammation leading to both local and systemic tissue injury. Although no studies have addressed whether mechanical ventilation is capable of altering lung cellular function leading to production of inflammatory mediators and lung injury, there is some evidence in the literature to support this concept. Clinical studies of adults developing ARDS have noted an association between lung inflammatory mediators and development of physiologic abnormalities [82]. Studies in a rabbit model of ARDS have found that conventional mechanical ventilation as opposed to high-frequency oscillatory ventilation (HFOV) led to increased neutrophil infiltration and activation, and increased lung lavage levels of

platelet-activating factor and thromboxane [85]. Concurrent with these physiological studies, research over the past decade has shown that mechanotransduction (ie, the conversion of a mechanical stimulus such as cell deformation into biochemical and molecular alterations) plays a crucial role in determining the structure and function of numerous tissues, including the lung. Studies in vitro and in vivo have found that both the degree and the pattern of mechanical stretch are important in determining cell responses [87]. Given that mechanical ventilation alters both the pattern and magnitude of lung stretch, it is not unreasonable to postulate that alterations in gene expression or cellular metabolism may arise. Specific patterns of ventilation can produce or magnify the inflammatory response in the lung, and thus provide a mechanism whereby mechanical ventilation could lead to lung injury and contribute to the development of a systemic inflammatory response [85].

A tidal breath delivered to an injured lung preferentially will follow the path of least resistance and inflate the more compliant, nondependent alveoli. When large tidal volumes are delivered, this can lead to overdistension of such alveoli and aggravate injury, by a process termed volutrauma. Injury to alveoli in the poorly compliant dependent lung also can be aggravated by a suboptimal ventilation strategy. If insufficient peak end-expiratory pressure (PEEP) is applied, dependent alveoli are subjected to cyclic opening and closing, which leads to injury through a process termed atelectrauma. Therefore, an optimal lung protective strategy should use inspiratory volumes that avoid overinflation of nondependent alveoli, yet provide enough PEEP to prevent the atelectrauma caused by cyclic derecruitment of dependent alveoli [86,88]. When a conventional ventilator is used, such a protective strategy often will result in lower minute ventilation, higher levels of $Paco_2$, and controlled respiratory acidosis or permissive hypercapnia. Although usually well tolerated in adults and pediatric patients with ARDS, permissive hypercapnia has not been well-studied in PPHN [88].

High-frequency ventilation can be used as a lung protective strategy in neonates who have HRF [88]. During HFOV, small tidal volumes are used at supraphysiologic rates to support gas exchange. If adequate mean airway pressure is used to recruit and maintain alveolar patency, the small magnitude of volume oscillations will neither cause overdistension of alveoli nor allow for derecruitment during expiration, thus avoiding the upper and lower limits of the pressure/volume curve. Because oxygenation and ventilation are not coupled directly during HFOV, it can be used as a lung protective strategy and achieve physiologic levels of $Paco_2$, reducing concerns about the potentially deleterious effects of acidosis in neonates who have PPHN [7,89–91].

The relationship between ventilation strategy and the development and progression of lung injury recently was demonstrated by Rotta and colleagues in a small animal model of lung injury [85]. Compared with standard ventilation, two distinct lung protective strategies, low tidal volume with PEEP and HFOV, were associated with improved oxygenation, attenuation

of inflammation as measured by tracheal fluid protein, elastase, tumor necrosis factor alpha and pulmonary leukostasis, and decreased lung injury. Animals treated with HFOV experienced less hemodynamic instability compared with the other experimental groups.

Ventilator settings should be adjusted to maintain normal expansion (ie, approximately 8 to 9 ribs) on chest radiograph. Monitoring of pulmonary mechanics may be helpful in avoiding overexpansion, which can contribute to elevated pulmonary vascular resistance and aggravate right-to-left shunting. In infants with severe pulmonary parenchymal disease who require high-peak inspiratory pressures, HFOV should be considered to reduce barotrauma [88]. Only two prospective randomized studies have compared HFOV with conventional ventilation in late preterm and term infants with acute HRF [7,92]. Neither showed a reduction in mortality or the need for ECMO, although HFOV, using a high volume strategy, can be used as an effective rescue therapy for some of these infants.

Of equal importance is determining the target arterial blood gas values. Pa_{O_2} levels of 50 to 60 mm Hg typically provide for adequate oxygen delivery. Aiming for significantly higher Pa_{O_2} concentrations may lead to increased ventilator support and lung injury. The use of hyperventilation first was described by Drummond and colleagues [93]. Forced alkalosis, using sodium bicarbonate, and hyperventilation became popular therapies because of their ability to produce acute pulmonary vasodilation and increases in Pa_{O_2}. Walsh-Sukys and colleagues [80] reviewed the management of PPHN and reported on unproven therapies (ie, hyperventilation, continuous infusion of alkali, sedation, paralysis, inotrope administration, and vasodilator drugs) used before widespread use of inhaled nitric oxide (iNO). No specific therapy was clearly associated with a reduction in mortality. Hyperventilation reduced the risk of ECMO without increasing the need for oxygen at 28 days of age. Hypocarbia, however, constricts the cerebral vasculature and reduces cerebral blood flow, and alkalosis and hypocarbia have been associated with later neurodevelopmental deficits, including a high rate of sensorineural hearing loss. The use of alkali infusion was associated with increased use of ECMO and an increased need for oxygen at 28 days of age. Successful management of infants with HRF without using alkalinization has been reported by Wung and colleagues [94] in a series of 15 neonates in whom a strategy designed to maintain Pa_{O_2} at 50 to 70 and Pa_{CO_2} at less than 60 resulted in excellent outcome and a low incidence of chronic lung disease.

Surfactant replacement

Exogenous surfactant therapy is another promising adjunctive treatment for late preterm and term neonates who have severe HRF. There is evidence that surfactant deficiency contributes to decreased lung compliance and

atelectasis in some patients who have PPHN [9,95–115]. Recent studies have suggested that exogenous surfactant therapy can cause sustained clinical improvement in late preterm and term infants with pneumonia and meconium aspiration syndrome and reduce the duration of ECMO [8,9,96,97,101,106,108,110,115–118]. A randomized multi-center trial demonstrated that treatment with surfactant decreased the need for ECMO in late preterm and term newborns with respiratory failure. Subset analysis, however, showed that the decrease in ECMO use was limited to patients treated earlier in the course of their disease (OI less than or equal to 22) [8]. Surfactant treatment does not appear to be effective in patients who have advanced HRF; however, by improving lung inflation, surfactant treatment may augment the response to inhalational vasodilators such as iNO [116].

Management of pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn is associated with increased pulmonary vascular resistance and leads to hypoxemia secondary to right-to-left shunting by means of fetal pathways and V/Q mismatching. Numerous treatments have been advocated to reduce pulmonary vascular resistance, beginning with the use of tolazoline by Goetzman and colleagues [119].

The physiologic rationale for iNO therapy for treating neonatal HRF is based on its ability to achieve potent and sustained pulmonary vasodilation without decreasing systemic vascular tone. The use of intravenous vasodilator drugs such as tolazoline and sodium nitroprusside in PPHN has had limited success because of systemic hypotension and inability to achieve or sustain pulmonary vasodilation [120]. The ability of iNO therapy to selectively lower pulmonary vascular resistance (PVR) and decrease extrapulmonary right-to-left shunting accounts for the immediate improvement in oxygenation observed in newborns who have PPHN [121,122]. As described in children and adults with severe respiratory failure [123,124], oxygenation also can improve during iNO therapy in newborns who do not have extrapulmonary right-to-left shunting [10]. Low-dose iNO therapy can improve oxygenation by redirecting blood from poorly aerated or diseased lung regions to better-aerated distal air spaces, thereby improving V/Q matching [125].

In addition to its effects on vascular tone and reactivity, other physiologic targets for iNO therapy in HRF may include direct effects on lung inflammation, vascular permeability, thrombosis in situ and pulmonary remodeling [126]. Although laboratory studies initially suggested that NO can potentiate lung injury by promoting oxidative stress [127,128], surfactant inactivation, and stimulating inflammation, more recent studies have demonstrated striking antioxidant and anti-inflammatory effects in models of lung injury [129–133]. These findings suggest that low-dose iNO therapy

may reduce lung inflammation and edema, as well as improve surfactant function in neonates with HRF, but these effects remain clinically unproven [126].

HRF in the late preterm and term newborn represents a heterogeneous group of disorders, and disease-specific responses have been described. Patients who have idiopathic PPHN show immediate improvement in oxygenation in response to iNO therapy, while patients with predominantly intrapulmonary shunting (eg, RDS) have less dramatic responses [91,134]. Several pathophysiologic disturbances contribute to hypoxemia in the newborn infant, including cardiac dysfunction, airway and pulmonary parenchymal abnormalities, and pulmonary vascular disorders. In some newborns who have HRF, only a single mechanism is operative, but in most, several of these mechanisms apply. The relative contribution of each mechanism may vary over time and dictate the use of different therapeutic modalities to reverse the hypoxemia [125].

Available evidence from clinical trials supports the use of iNO in late preterm (at least 34 weeks gestation) and term newborns with hypoxemic respiratory failure who require mechanical ventilation and high inspired oxygen concentrations [6,10,135,136]. A recent meta-analysis of six randomized controlled trials showed that about 50% of infants will have clinically significant increases in oxygenation within 60 minutes after initiating iNO [137]. Clinical trials of iNO in the newborn have incorporated ECMO treatment as an end point and have shown a 35% to 40% reduction in the need for ECMO in late preterm and term infants treated with iNO. Although one of the pivotal studies used to support the new drug application for iNO therapy included infants with a postnatal age up to 14 days, the average age at enrollment was 1.7 days. Currently, clinical trials support the use of iNO before treatment with ECMO, usually within the first week of life. Clinical experience, however, suggests that iNO may be of benefit as an adjuvant treatment after ECMO therapy in patients with sustained pulmonary hypertension (eg, congenital diaphragmatic hernia) [138]. Thus postnatal age alone should not define the duration of therapy in cases in which prolonged treatment could be beneficial.

Although clinical trials commonly used an OI greater than 25 for enrollment, the mean OI at study entry in multi-center trials approximated 40. A trial of the early institution of iNO in late preterm and term neonates with HRF at an OI of 15 to 25 resulted in improved oxygenation, with fewer iNO treated infants progressing to an OI greater than 40 [139]. There was no improvement in outcome, however (ie, mortality, morbidity, or the need for ECMO support) when compared with initiation of iNO at an OI greater than 25. Echocardiographic evidence of PPHN was a criteria for enrollment in all but the Neonatal Inhaled Nitric Oxide Study (NINOS) trial [6]. Echocardiography was performed before randomization in 97% infants of enrolled in the NINOS trial, and 78% had evidence of pulmonary hypertension. There was no difference in primary outcome or response to

iNO based on the presence of echocardiographic evidence of pulmonary hypertension in this large series. Current multi-center studies suggest that indications for treatment with iNO include an OI greater than 25 even in the absence of echocardiographic evidence of extrapulmonary right-to-left shunting.

The first studies of iNO treatment in late preterm and term newborns reported initial doses that ranged from 80 to 20 ppm. The rationale for doses used in these clinical trials was based on concentrations that had previously been found to be effective in animal experiments. Roberts and colleagues reported that brief inhalation of nitric oxide (NO) at 80 ppm improved oxygenation in patients who had PPHN, but this response was sustained in only one patient after NO was discontinued [140]. In the second report, rapid improvement in oxygenation in neonates who had severe PPHN also was demonstrated, but this was achieved at lower doses (20 ppm) for 4 hours [121]. This study also reported that decreasing the iNO dose to 6 ppm for the duration of treatment provided sustained improvement in oxygenation. The relative effectiveness of low-dose iNO in improving oxygenation in newborns with severe PPHN was corroborated in a dose–response study by Finer and colleagues [141]. Immediate improvement in oxygenation during treatment was not different with doses of iNO ranging from 5 to 80 ppm. These laboratory and clinical studies established the iNO dosing protocols for subsequent randomized clinical trials in newborns. The initial dose in the NINOS trial was 20 ppm, but the dose was increased to 80 ppm if the improvement in Pao_2 was $<$ 20 mm Hg. In this study, only 3 of 53 infants (6%) who failed to response to 20 ppm had an increase in Pao_2 $>$ 20 mm Hg when treated with 80 ppm iNO [6]. Whether a progressive increase in Pao_2 would have occurred with continued exposure to 20 ppm could not be determined with this study design. Roberts et al initiated treatment with 80 ppm iNO and subsequently decreased the iNO concentration if oxygenation improved; thus, the effects of lower initial iNO doses could not be evaluated, and the effects on ECMO use were not evaluated [10]. Only one trial evaluated the effects of sustained exposure to different doses of iNO in separate treatment groups of newborns. Davidson and colleagues [136] reported the results of a randomized controlled dose–response trial in late preterm and term newborns with PPHN. In their study, patients randomly were assigned to treatment with placebo or 5, 20, or 80 ppm NO. Each iNO dose improved oxygenation compared with placebo, but there was no difference in responses between groups. In the 37 patients treated with 80 ppm, however, methemoglobinemia levels greater than 7% occurred in 35% of patients, and inspired nitrogen dioxide concentrations greater than 3 ppm were reported in 19% of patients. Therefore, the available evidence supports initiation of iNO at a dose of 20 ppm in late preterm and term newborns who have HRF. Finer and colleagues [142] reported their experience with very low-dose iNO (1 to 2 ppm) in a small series of late preterm and term neonates who had HRF. There was no significant difference

in the initial response to low-dose versus high-dose iNO, although dose increases were required more often in the low-dose group. Among patients who did not respond to the initial iNO dose, 100% and 83% responded at higher doses of iNO for the low- and high-dose groups, respectively. No differences in mortality, PPHN-associated morbidity, or the need for ECMO were demonstrated between treatment groups.

In multi-center clinical trials of iNO therapy, the typical duration of iNO treatment has been less than 5 days, which parallels the clinical resolution of PPHN. Individual exceptions occur, however, particularly in cases of pulmonary hypoplasia. If iNO is required for longer than 5 days, investigations into other causes of pulmonary hypertension should be considered (eg, alveolar capillary dysplasia, pulmonary alveolar proteinosis, or undiagnosed congenital heart disease), particularly if discontinuation of iNO results in suprasystemic elevations of pulmonary artery pressure as determined by echocardiography. No controlled data are available to determine the maximal safe duration of iNO therapy.

After improvement in oxygenation occurs with the initiation of iNO therapy, strategies for weaning the iNO dose become important. Numerous approaches have been used. Generally, oxygenation does not decrease significantly until discontinuation of iNO treatment. In one study, iNO was reduced from 20 to 6 ppm after 4 hours of treatment without acute changes in oxygenation [135]. In another trial, iNO was reduced in a stepwise fashion to as low as 1 ppm without changes in oxygenation [6,136]. Weaning iNO is a different process than discontinuation of iNO therapy. Early clinical studies reported rapid and sometimes dramatic decreases in oxygenation and increases in PVR after abrupt cessation of iNO [136]. These responses are often mild and transient, and many patients with decreased oxygenation after iNO withdrawal will respond to brief elevations of FiO_2 and careful observation [143,144]. Discontinuation of iNO, however, can be associated with life-threatening elevations of PVR, profound desaturation, and systemic hypotension caused by decreased cardiac output even in those neonates whose oxygenation failed to improve on iNO [145]. In patients who deteriorate after withdrawal of iNO, restarting iNO treatment generally will cause rapid clinical improvement. Several possible mechanisms contribute to the rebound effect. First, iNO may downregulate endogenous NO production, which contributes directly to the severity of vasospasm after iNO withdrawal. Second, decreased vascular sensitivity to NO caused by alterations in other components of the NO-cyclic guanosine monophosphate (cGMP) pathway, such as decreased soluble guanylate cyclase or enhanced phosphodiesterase 5 activities, may contribute to vasospasm after NO withdrawal. In a prospective study of patients who had undergone heart surgery with marked hemodynamic changes after iNO withdrawal, sildenafil (cGMP-specific phosphodiesterase-type V inhibitor) inhibited the adverse effects of acute iNO withdrawal [146]. These findings led to the speculation that sildenafil may sustain smooth muscle cGMP content and that persistent

phosphodiesterase type V activity may contribute to the rebound pulmonary hypertension after iNO withdrawal. Alternatively, the rise in PVR and drop in oxygenation after iNO withdrawal simply may represent the presence of more severe underlying pulmonary vascular disease with loss of treatment effect of iNO. The sudden increase in pulmonary artery pressure after rapid withdrawal of vasodilator therapy is not unique to iNO and has been observed in other clinical settings, such as prostacyclin withdrawal in patients who have primary pulmonary hypertension [147].

Pharmacologic augmentation of the iNO response also may prove to be effective in some patients who have PPHN. Inhaled NO causes pulmonary vasodilation by stimulating soluble guanylate cyclase and increasing cGMP content in vascular smooth muscle. Smooth muscle cGMP content is regulated further by cGMP-specific phosphodiesterase type V, which inactivates cGMP by hydrolysis. Whether the inability to sustain cGMP contributes to the failure of some patients with PPHN to respond or to sustain improved oxygenation during iNO therapy is uncertain. Early clinical experience with dipyrdamole, which has phosphodiesterase type V inhibitory activity, has been variable [148–150]. Although dipyridamole may enhance the response to iNO in some patients, its effects are variable and are not selective for the pulmonary circulation. Recent studies with sildenafil, a more selective phosphodiesterase type V antagonist, appear more promising and may lead to novel clinical strategies to enhance the treatment of pulmonary hypertension [151–153].

Considering the important role of parenchymal lung disease in this condition, pharmacologic pulmonary vasodilation alone would not be expected to cause sustained clinical improvement in many cases. Moreover, patients not responding to iNO can show marked improvement in oxygenation with adequate lung inflation alone. High success rates in early studies were achieved by withholding iNO treatment until attempts were made to optimize ventilation and lung inflation with mechanical ventilation [6,10,135,136]. These early studies demonstrated that the effects of iNO may be suboptimal when lung volume is decreased in association with pulmonary parenchymal disease. Atelectasis and air space disease may decrease the effective delivery of iNO to its site of action in terminal lung units. In cases complicated by severe lung disease and underinflation, pulmonary hypertension may be the result of the adverse mechanical effects of underinflation on pulmonary vascular resistance. Aggressive ventilation may result in overinflation because of inadvertent PEEP and gas trapping and may elevate pulmonary vascular resistance caused by vascular compression. This commonly complicates the treatment of infants with asymmetric lung disease or airway obstruction, as observed in meconium aspiration syndrome. In newborns with severe lung disease, HFOV frequently is used to optimize lung inflation and minimize lung injury. A randomized multi-center trial demonstrated that treatment with HFOV plus iNO was often successful in patients with severe PPHN who did not respond to HFOV or iNO alone

and that differences in responses were related to the underlying diagnosis [92]. For patients with PPHN complicated by severe lung disease, response rates for HFOV plus iNO were better than those for HFOV or iNO alone.

In contrast, for patients who have idiopathic PPHN, both iNO and HFOV plus iNO were more effective than HFOV alone. This response to combined treatment with HFOV plus iNO is likely because of improvement in both intra- and extrapulmonary right-to-left shunting based on maneuvers that simultaneously recruit and sustain lung volume and augment NO delivery to its site of action.

Published reports on the use of iNO in ECMO centers have not substantiated early concerns that iNO would affect outcome adversely by delaying ECMO use [3,6,135,136,139]. Decreased ECMO use with iNO treatment in multi-center RCTs has not been associated with an increase in mortality, neurologic injury, or bronchopulmonary dysplasia. Indeed, in one trial, iNO treatment was associated with improved pulmonary outcomes [135]. In another study, the median time from randomization to treatment with ECMO was 4.4 and 6.7 hours for the control and iNO groups, respectively [136]. Although this difference was statistically significant, there were no apparent adverse consequences caused by the delay. More recently, the use of iNO before initiation of ECMO was shown to improve ECMO outcomes by decreasing the need for cardiopulmonary resuscitation before ECMO cannulation [154]. Although marked improvement in oxygenation occurs in many late preterm and term newborns with severe PPHN, sustained improvement may be compromised in some patients by progressive worsening of pulmonary compliance or cardiovascular function necessitating referral for ECMO support. Withdrawal of iNO during transport to an ECMO center may lead to acute decompensation [136,145]. In such cases, iNO provides an important therapeutic bridge, ensuring stability during transport. When progressive deterioration in oxygenation occurs during iNO treatment in institutions that cannot offer more advanced rescue therapy, provisions must be in place to accomplish transport to the ECMO center without interruption of iNO treatment.

Other vasodilators that have not yet been shown to have selective or clinically beneficial effects when given systemically are being studied for use by inhalation. They include tolazoline, prostaglandin derivatives, and nitrosodilators [155–159]. The most appropriate drug would have a direct immediate effect on the pulmonary vasculature and be degraded rapidly by circulating enzymes to prevent systemic effects even after prolonged treatment. The vasodilating actions of prostacyclin are dependent on a receptor-mediated increase in intracellular cyclic adenosine monophosphate. This suggests that there may be synergy with iNO, whose actions are mediated through cGMP. Combined treatment with iNO and prostacyclin therefore may have even greater benefits, and isolated reports and small case series of successful combined treatment of refractory PPHN have been published [157,160].

Extracorporeal membrane oxygenation

Recent data from the ELSO Neonatal Registry show a decrease in the use of ECMO support, presumably because of the effectiveness of the previously described treatments such as lung protective ventilation, iNO, and exogenous surfactant administration in late preterm and term infants [161]. Not all infants will respond to these new treatments, however. Extracorporeal life support is used to treat acute respiratory failure when other treatment modalities have failed. ECMO was shown to improve the survival in late preterm and term infants with severe respiratory failure in at least two single institution RCTs [162,163]. Subsequently, the United Kingdom collaborative randomized trial of neonatal ECMO and follow-up studies reported that ECMO significantly reduced the risk of death without an increase in severe disabilities [164]. In this study, 30 of 93 infants in the ECMO group died, compared with 54 of 92 in the conventional care group.

Infants with diaphragmatic hernia had a poorer outcome than other patients receiving extracorporeal membrane oxygenation, with a survival rate of 62% compared with 83% in infants with other diagnoses. Venovenous ECMO, which is used less frequently, is preferable to venoarterial ECMO in acute respiratory failure, as it avoids cannulation of the carotid artery and seems to have fewer complications [165,166]. Newer techniques for extracorporeal gas exchange, such as the single lumen cannula push-pull method, known as AREC (assistance respiratoire extracorporelle), provides effective support in smaller neonates, is faster to apply since the cannulation is generally percutaneous, and is simpler to operate [167].

Consideration of ECMO therapy should include an evaluation of risks versus benefits because of the invasive nature of the therapy and the need for heparinization. Usual criteria for ECMO support include:

- 34 weeks gestation or greater
- Weight 2000 g or more
- No major intracranial hemorrhage
- Reversible lung disease, on mechanical ventilation for no more than 14 days
- No lethal congenital anomalies
- Refractory hypoxemia
- Circulatory collapse

Prematurity is associated with increased morbidity and mortality rates related to ECMO and has led to the exclusion of very premature infants from consideration for bypass support. In 1992, Revenis and colleagues [78] reported their experience with lower birth weight infants (2000 to 2500 gm) treated with ECMO at a single center. Mortality was significantly higher in the lower birth weight infants (relative risk [RR] 3.45, confidence interval [CI] 1.68 to 5.79) compared with infants with normal birth weights. For infants who had RDS, mortality was 56% for the lower birth weight versus

8% for the normal birth weight group ($P < .01$). The most frequent cause of death was intracranial hemorrhage. The overall incidence of any neuroimaging abnormality and the risk of developmental delay among survivors was significantly greater among the lower birth weight infants. More recently, the role of postconceptual age as an independent predicator of intracranial hemorrhage in premature neonates treated with ECMO has been published [80]. These results were corroborated further by the authors' recent review of data from the ELSO Neonatal Registry detailed earlier.

The late preterm infant with refractory hypoxemia should be referred for bypass support if he or she fails to respond to other rescue therapies. The timing of referral to an ECMO center is critical. As recently as 10 to 15 years ago, mortality for neonatal HRF was 40% to 60%, with an incidence of major neurologic handicap of 15% to 60% [164,168]. If all available rescue therapies including ECMO are used, mortality is currently less than 20% to 25%, and the incidence of major neurologic handicap for surviving infants is approximately 15% to 20%. Early consultation and discussion with the ECMO center is recommended strongly. Guidelines for consultation are available at: http://www.elso.med.umich.edu/.

Summary

In the United States, a significant number of babies each year are delivered at late preterm gestations, and up to 50% of these deliveries occur by cesarean section. Of these, a significant number of infants develop severe hypoxic respiratory failure, resulting in need for additional treatments like ventilation, surfactant, inhaled nitric oxide, and ECMO. There is an urgent need for preventive and therapeutic interventions that can help in optimizing the outcome of this vulnerable population.

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