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Review Article

Neonatal air leak syndrome and the role of high-frequency ventilation in its prevention

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Abstract

Air leak syndrome includes pulmonary interstitial emphysema, pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema, and systemic air embolism. The most common cause of air leak syndrome in neonates is inadequate mechanical ventilation of the fragile and immature lungs. The incidence of air leaks in newborns is inversely related to the birth weight of the infants, especially in very-low-birth-weight and meconium-aspirated infants. When the air leak is asymptomatic and the infant is not mechanically ventilated, there is usually no specific treatment. Emergent needle aspiration and/or tube drainage are necessary in managing tension pneumothorax or pneumopericardium with cardiac tamponade. To prevent air leak syndrome, gentle ventilation with low pressure, low tidal volume, low inspiratory time, high rate, and judicious use of positive end expiratory pressure are the keys to caring for mechanically ventilated infants. Both high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) can provide adequate gas exchange using extremely low tidal volume and supraphysiologic rate in neonates with acute pulmonary dysfunction, and they are considered to have the potential to reduce the risks of air leak syndrome in neonates. However, there is still no conclusive evidence that HFOV or HFJV can help to reduce new air leaks in published neonatal clinical trials. In conclusion, neonatal air leaks may present as a thoracic emergency requiring emergent intervention. To prevent air leak syndrome, gentle ventilations are key to caring for ventilated infants. There is insufficient evidence showing the role of HFOV and HFJV in the prevention or reduction of new air leaks in newborn infants, so further investigation will be necessary for future applications.

Keywords: air leak syndrome; high-frequency oscillatory ventilation; neonate; pneumothorax; pulmonary interstitial emphysema

1. Introduction

Respiratory failure is a major cause of morbidity and mortality in neonatal critical care. During the past several decades, there has been substantial advancement in the area of neonatal respiratory care. The use of nasal continuous positive airway pressure (NCPAP), conventional mechanical ventilation (CMV), exogenous surfactant supplement, high-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation (HFJV), and inhaled nitric oxide have improved the general outcome for neonates with severe respiratory failure of different causes. However, air leak syndrome is still present in critical neonates, even those neonates who have already undergone these advanced ventilatory techniques.

Air leak syndrome is defined as that phenomenon when air escapes from the tracheobronchial tree and collects in various body spaces where it is not normally present. The escaping air tracks along various pathways and localizes in different body spaces leading to different types of air leaks, including pulmonary interstitial emphysema (PIE), pneumothorax, pneumomediastinum, pneumopericardium, pneumoperitoneum,

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subcutaneous emphysema, and systemic air embolism (Table 1).[1,2] The pathways of air leaking from the tracheobronchial tree are shown in Fig. 1.[1]

The most common cause of air leak syndrome is inadequate mechanical ventilation on the fragile and immature lungs. Therefore, air leak syndrome occurs more routinely during the neonatal period than any other age,[3] and the incidence is inversely related to the birth weights of newborn infants. Air leak syndromes occur in 1% to 2% of all newborns, and the incidence rises to as high as 40% among infants on mechanical ventilation in some situations and is the highest in the infants with meconium aspiration syndrome.[1] The common risk factors of air leak syndrome are listed in Table 2.[1,4,5]

However, infants may still develop air leaks even without mechanical ventilation. In the report of Migliori et al,[6] 10.3% of infants treated with NCPAP developed pneumothorax.[6] The authors suggested that a marked increase in the requirement of oxygen (FiO_2 increase: 0.4 or above) during the first 24 hours of NCPAP should be highly suggestive of the development of a new pneumothorax.[6] In addition, traumatic deliveries or endotracheal intubation may atypically induce neonatal tracheal injury or perforation, and that may cause subcutaneous emphysema and/or pneumomediastinum.[7]

Air leaks have been known as a risk factor in increasing the mortality rate of infants with respiratory distress syndrome (RDS).[5,8] After review of 552 newborn infants with RDS, Sly et al reported that air leaks developed in 22% of them,[5] and 87% were under mechanical ventilatory treatment. The mortality rate significantly increased from 12% in infants without air leaks to 31% in infants with air leaks.[5] Therefore, prevention, early diagnosis and adequate management for the development of air leak syndromes are crucial in caring newborn infants with severe pulmonary dysfunction.

2. Classification

2.1. PIE

PIE occurs when there is collection of gases outside the normal air passages. There is an escape of air into pulmonary interstitium, lymphatic and venous circulation, or secondary to rupture at the junction of the bronchiole and alveolar duct. PIE commonly occurs in conjunction with RDS, but other predisposing etiological factors, such as meconium aspiration syndrome or sepsis, may precipitate its occurrence. In the general neonatal intensive care unit population, 2% to 3% of all infants develop PIE. However, in premature infants with RDS, the incidence increases to 20% to 30%.[9] High risk premature infants with high ventilatory settings of CMV are the major risk factors of PIE.

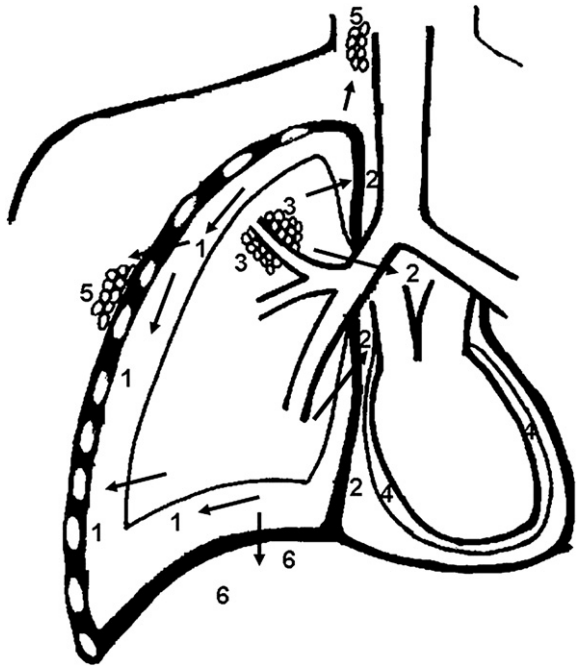

Fig. 1. Illustrations of the air leaking from the tracheobronchial tree. 1, pneumothorax; 2, pneumomediastinum; 3, pulmonary interstitial emphysema; 4, pneumopericardium; 5, subcutaneous emphysema; 6, pneumoperitoneum. Arrows: directions of air leaks. (Modified from Professor Jen-Tien Wung, Babies & Children's Hospital of New York, Columbia University, New York, NY, USA.)

The diagnosis of PIE is mainly radiographic and pathologic. The anterior-posterior view of chest radiography may show linear, oval, or spherical cystic air-containing spaces (Fig. 2). The heart may become reduced in size, and lung volume can be larger than its customary characteristic. It can present localized or diffused distribution at the lung field, with possible unilateral or bilateral involvement. Furthermore, it can also be associated with the presence of pneumothorax. The clinical manifestation of PIE is impairment of gas exchange with hypercarbia and hypoxia, with an increased setting necessary for ventilator support.

Table 1
Classification of air leak syndrome.

Pulmonary interstitial emphysema (PIE)
Pneumothorax
Pneumomediastinum
Pneumopericardium
Subcutaneous emphysema
Pneumoperitoneum
Systemic air embolism

Table 2
Risk factors of neonatal air-leak syndrome.

Prematurity
Very low birth weight
Low Apgar score and need of resuscitation
Positive pressure ventilation
Use of high peak inspiratory pressure
Use of high tidal volume
Use of high inspiratory time
Respiratory distress syndrome
Meconium aspiration syndrome
Amniotic fluid aspiration
Pneumonia
Pulmonary hypoplasia

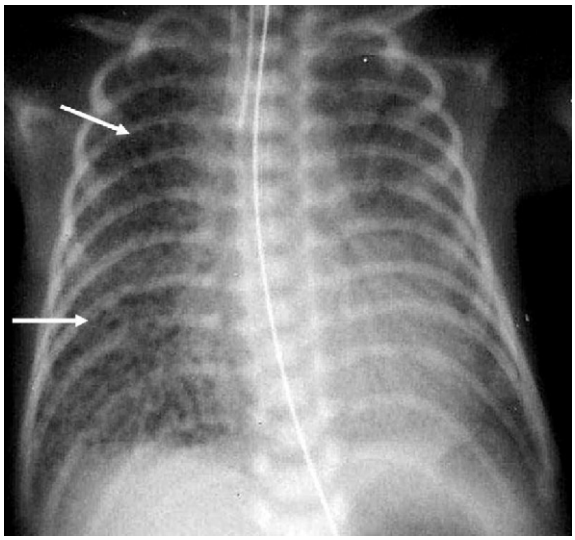

Fig. 2. A chest radiograph of a premature infant with respiratory distress syndrome and pulmonary interstitial emphysema at the right lung field (arrows). The lung is overexpanded to the eleventh rib.

The potential complications of PIE include epithelialization of the interstitial air pockets, loss of pulmonary compliance, air embolus formations in pulmonary venous circulation, pneumothorax, and the formation of bronchopulmonary dysplasia/chronic lung disease.

If the patient is not critical, PIE is usually managed conservatively, with gentle ventilation. The decubitus position with the affected side down may be helpful. Sometimes, selective intubation of the main bronchus on the uninvolved side for at least 48 hours may also be beneficial.[2] In addition, a technique of single-lung ventilation using a Swan-Ganz catheter to block the main bronchus on the disease side with prominent PIE has been successfully used on neonates unresponsive to conventional therapy.[10] Lobectomy is rarely used to treat the severely complicated PIE. Furthermore, HFOV or HFJV are additional options that can be employed to reduce the air-leak severity.

2.2. Pneumothorax

Pneumothorax refers to the presence of gas in the pleural cavity between the visceral and parietal pleura, which results in violation of the pleural space. It has been reported to have an incidence of 6% to 10% in very-low-birth-weight (VLBW) premature infants, and around 1% in term neonates.[3,11–13]

The initial clinical appearance of mild form pneumothorax may be asymptomatic. As the condition progresses, infants may suffer gradual deterioration of arterial blood gases, with an increased oxygen or ventilator requirement. The infant may appear agitated, or have unstable vital signs including an initial increase in blood pressure. As the air leak progresses, progressive respiratory distress, including rapid breathing, grunting, nasal flaring, and chest wall retractions may become significant. When tension pneumothorax occurs, there will be acute and severe cyanosis, which combines with the onset of acute bradycardia, hypotension, decreased pulse pressure and peripheral perfusion, barrel shaped chest, and acute abdominal distension.

Diagnosis of pneumothorax is usually made by radiography (Fig. 3). However, a diagnosis of tension pneumothorax should result in immediate emergency attention, since death can occur even before diagnostic imaging can be completed. When pneumothorax is suspected, anterior–posterior radiographic views should be taken. Small pneumothoraces can be better seen with lateral decubitus film, with the affected side up. Sometimes, the costophrenic angle may be abnormally deepened when the pleural air collects laterally, producing the deep sulcus sign.[14] Use of a chest transillumination test with high intensity light may quickly help to establish a preliminary diagnosis in neonates, and excessive light can be transmitted at the affected side (Fig. 4).[1,15]

Medical management of pneumothorax depends on its severity. When patients are asymptomatic and not on ventilator support, there is no need for specific management. In full-term neonates, not in premature infants, with small uncomplicated pneumothorax, a support of 100% oxygen for nitrogen washout may improve the resolution of pneumothorax in cases without mechanical ventilation. Emergent thoracentesis with needle aspiration is necessary to treat a symptomatic pneumothorax. The location of the aspirated site is at the third intercostal space in the midclavicular or anterior axillary line. Use of a 24-gauge angiocatheter or a scalp vein needle attached to 20 mL syringe with a stopcock is suggested for the emergent aspiration of leaked air from the pleural cavity.[16] In addition, it has been reported to treat expectantly without initial chest-tube placement in some ventilated neonates with pneumothorax if the vital signs are stable.[17]

Chest tube insertion for definitive drainage is usually necessary in the case of tension pneumothorax and a pneumothorax that develops in a mechanically ventilated infant. A

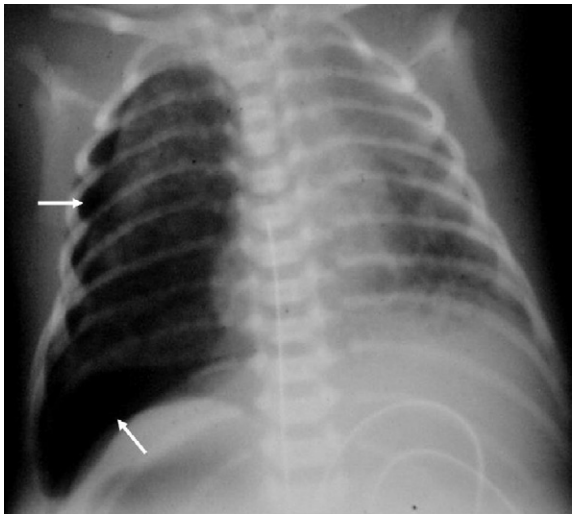

Fig. 3. A chest radiograph of a premature infant with right tension pneumothorax (arrows) and partial collapse of right lung. The mediastinum is shifted to the left side.

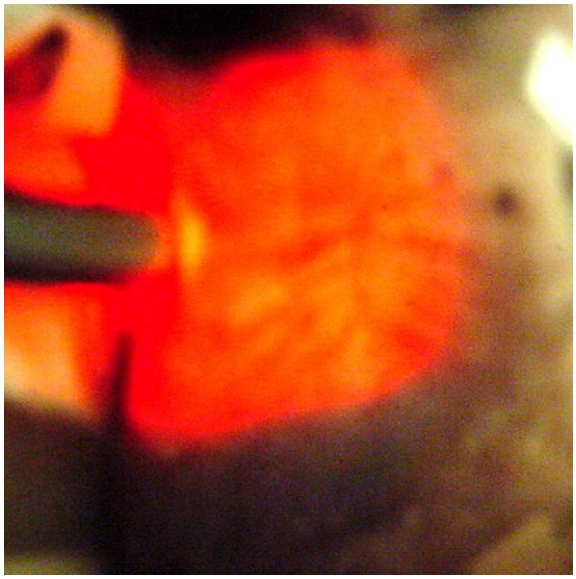

Fig. 4. Positive transillumination test on a premature infant with right pneumothorax. The right pleural cavity is transilluminated with bright red light. (Courtesy of Professor Jen-Tien Wung, Babies & Children's Hospital of New York, Columbia University, New York, NY, USA.)

8F to 12F catheter is adequate for a neonate. The chest tube insertion site can be at the midclavicular line of the second to third intercostal spaces or at the anterior to midaxillary line of the fourth to sixth intercostal spaces.[16,18] The chest tube can be connected with a negative pressure of 10 to 15 cmH_2O suctioning for promoting adequate drainage.[19] A chest radiograph to confirm the lung expansion condition and chest tube position is necessary after the procedures are completed. If there are any continuous air leaks with water vapor in the chest tube, lung perforation from chest tube placement or bronchopleural fistula from endotracheal suctioning should be considered. In these conditions, one-lung ventilation may be required, with thoracotomy and suturing of the bronchopleural fistula. After cessation of air leaks, place the chest tube under water seal for 24 hours. If there is no reaccumulation of air, remove chest tube during expiration if breathing spontaneously or during inspiration if on the ventilator. A further radiological confirmation after removal of the chest tube is necessary. In addition, percutaneous small bore pigtail catheters (8–10F) or a large size (18-gauge) venous catheter have been used for air drainage in neonates, but the potential risks of pulmonary perforation and catheter blockage are greater in premature infants.[20–23]

2.3. Pneumomediastinum

Pneumomediastinum is a condition where air leaks into the mediastinal space. The diagnosis is made on a chest radiograph, with a noted presence of hyperlucent areas around the heart border and between the sternum and the heart border.[15] If it is an isolated problem, most cases are asymptomatic and may resolve spontaneously under gentle respiratory care. The patient should be closely observed for the possibility of other air leaks, especially pneumothorax.

However, collection of any considerable volume of air in the mediastinal space may result in tachypnea and hypoxia. Distant heart sound may be found while confirming this with a stethoscope. Furthermore, bulging of the midthoracic area, distended neck veins, and low blood pressures may occur if the amount of air leak in the mediastinal space is serious enough to induce tamponade of the systemic and pulmonary veins.[15] When these conditions happen, pneumopericardium may also occur and be fatal without adequate decompression.

2.4. Pneumopericardium

Pneumopericardium is a rare condition caused by air in the pericardial space. In severe condition, it can cause cardiac tamponade that is life-threatening. Pneumopericardium typically occurs in a mechanically ventilated preterm infant with severe RDS who also has pneumothorax and/or PIE.

The onset of pneumopericardium is an abrupt onset of hemodynamic compromise due to cardiac tamponade. Tachycardia and a narrowed pulse pressure may be followed by bradycardia, hypotension, deteriorated respiratory distress, and cyanosis. The heart sound may be distant or difficult to be heard. The electrocardiogram may show low voltages with a small QRS complex.

The diagnosis of pneumopericardium is confirmed by chest radiograph. It may show a gas shadow surrounding the heart (Fig. 5).[1] In life-threatening situations in which pneumopericardium is strongly suspected, the diagnosis can be confirmed by a therapeutic pericardiocentesis.

The management of pneumopericardium is mainly close monitoring if it is asymptomatic. Ventilator adjusting to decrease pressure is necessary to minimize the severity of air

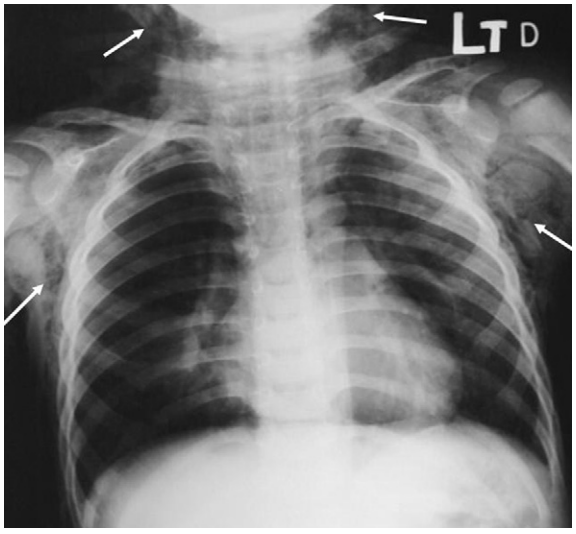

Fig. 5. A chest radiograph of a newborn infant with pneumopericardium (arrows). (Courtesy of Professor Jen-Tien Wung, Babies & Children's Hospital of New York, Columbia University, New York, NY, USA.)

leaks. Pericardial drainage is only applied on symptomatic infants for both diagnostic and therapeutic purposes.

2.5. Pneumoperitoneum

Pneumoperitoneum is an uncommon type of air leak. It occurs when extrapulmonary air gets into the peritoneal cavity. The diagnosis is typically made after review of an abdominal radiograph, and usually has little clinical significance. The abdominal x-ray may reveal a dark layer over the abdomen obscuring the normal bowel pattern. It must be differentiated from intraperitoneal air due to a perforated intra-abdominal organ. If it results from ruptured viscus, immediate surgical intervention is required. However, abdominal air of intrathoracic origin usually requires observation only.

2.6. Subcutaneopus emphysema

Subcutaneous emphysema is characterized by crepitus on physical examination by palpation. It typically occurs in the face, neck, axillary, or supraclavicular regions. On the radiographs, disseminated leaked air can be observed in the subcutaneous tissue (Fig. 6).[1] It is usually of no clinical significance, although large amount of air may cause tracheal compromise. Management is mainly observation and decreasing the ventilatory settings for its resolution.

2.7. Systemic air embolism

In systemic air embolism, the air rupturing from the alveoli enters directly into the pulmonary capillaries, after which the infant develops abrupt cyanosis and circulatory collapse. Air popping in the heart may be audible with a stethoscope. Air admixed with blood may also be withdrawn from the umbilical arterial catheter sampling. There is no specific treatment and this condition is invariably fatal.[1]

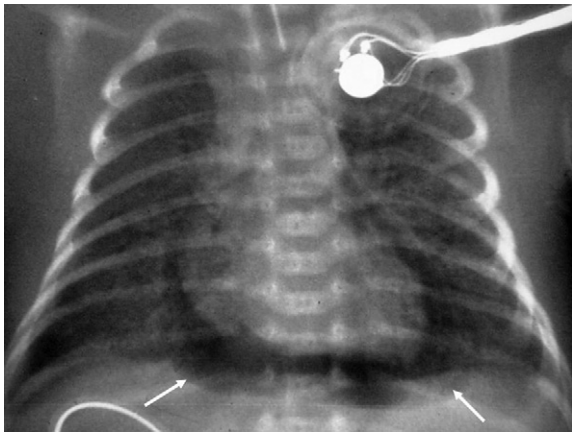

Fig. 6. A chest radiograph of a newborn infant with diffuse subcutaneous emphysema (arrows). There is leaked air disseminating in the subcutaneous tissue of neck, shoulder, chest wall, and bilateral axillary area.

3. Prevention of air-leak syndrome

3.1. Gentle ventilation

Gentle ventilation is the key to prevent air leak syndrome. In addition, gentle resuscitation in the delivery room is also important to reduce the incidence of air leak syndrome in high-risk newborns.[7,24]

The goal of mechanical ventilation is to achieve and maintain adequate pulmonary gas exchange, minimize the risk of lung injury, reduce patient work of breathing, and optimize the patient's comfort. The concept of ventilator-induced lung injury (VILI) was described by Hudson in 1999.[25] Volutrauma with the increase in vascular filtration and stress fractures of capillaries, epithelium, and basement membranes and biotrauma with increased proinflammatory cytokines and subsequent inflammatory reactions are the main problems (Fig. 7). Air leaks, pulmonary fibrosis and recurrent pulmonary infections may occur and cause mortality or chronic lung disease. Premature infants with antecedent lung injury are more prone to VILI. Gentle ventilation with the concept of permissive hypercapnia, low tidal volumes, low peak inspiratory pressure, high rate, and low inspiratory time (IT) all may be helpful in reducing air-leak syndrome.[26–28] Permissive hypercapnia and judicious use of NCPAP have been used in caring for high-risk newborn infants for a long time, with a relatively low incidence of air leaks and bronchopulmonary dysplasia.[1,29,30] There have been clinical trials further examining the concept of permissive hypercapnia in premature infants,[26,27] which found that the need for mechanical ventilation at 36 weeks post-conceptional age can be reduced from 16% to 1% in premature infants with permissive hypercapnia (maintaining $PaCO_2$ >52 mmHg).[27]

Kamlin conducted a meta-analysis on the role of IT in mechanically ventilated infants. Five studies (694 infants) were analyzed, and it was concluded that long IT (≥0.5 seconds) is significantly associated with the occurrence of air leaks [risk ratio (RR) 1.56, 95% confidence interval (CI) 1.25–1.94] and increased mortality rate (RR 1.26, 95% CI

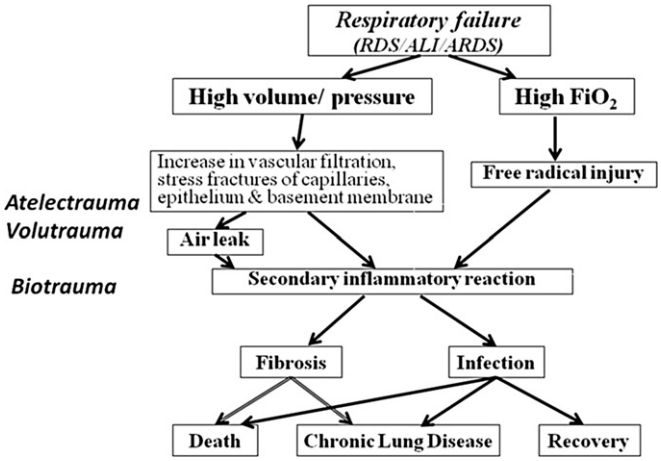

Fig. 7. Simplified injury mechanism of ventilator-induced lung injury.

1.00−1.59).[31] There was no significant impact on bronchopulmonary dysplasia, although all of the included studies were conducted prior the use of antenatal steroids, postnatal surfactant and HFOV. Consequently, there may be some difference currently.

In addition, Klinger et al has reported that pneumothorax in VLBW infants is associated with factors present on the day of pneumothorax and not with initial ventilation variables or initial severity of lung disease. They suggested that vigorous control of ventilation, including optimizing positive end-expiratory pressure and minimizing peak inspiratory pressure and the number of suction procedures, is required to decrease the risk of pneumothorax in VLBW infants.[11]

In the meta-analysis of Steven et al (6 studies, 664 participants), the use of early surfactant administration with brief ventilation (rapid extubation to NCPAP) may reduce the risk of air leak syndrome (RR 0.52, 95%CI 0.28−0.96).[32]

In considering of the role of continuous distending pressure (CDP) in RDS, a systemic review by Ho et al summarized that the use of CDP either as CPAP by mask, nasal prong, nasopharyngeal tube, or endotracheal tube, or continuous negative pressure via a chamber enclosing the thorax and lower body is associated with an increased rate of pneumothorax (summary RR 2.36, 95%CI 1.25−5.54). Nonetheless, it did decrease the rate of failed treatment and overall mortality.[33] Therefore, a judicious use of CDP is crucial in treating premature infants.

3.2. Role of high-frequency ventilations

High-frequency ventilations with extremely low tidal volumes and supraphysiologic rates have been successfully demonstrated to reduce lung injury in experimental models of acute lung injury.[34,35] Both HFOV and HFJV have been applied on neonates with acute pulmonary dysfunction.[19]

3.2.1. HFOV

In 1972, Lunkenheimer et al[36] first discovered that HFOV could maintain normocapnia by oscillating small volumes of air into animals' lung at a frequency of 23-40 Hz. The first report of HFOV use as applied to humans was published in 1981 by Marchak et al.[37] Since then, several clinical trials investigating the role of HFOV to treat surfactant-deficient RDS in premature infants or other types of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) have taken place. Currently, there is dramatic increase in clinical use of HFOV in rescuing infants suffering from respiratory failure.[19,38]

HFOV needs an electromagnetically driven diaphragm or a piston pump to generate oscillating movements of diaphragm, and induces active inspirations and expirations. The oscillators can deliver extremely low tidal volumes (1−3 mL/kg) and very high ventilatory rates (210−900 breaths/min).[19] It is able to ventilate patients with adequate lung volume and minimize the risks of volutrauma and atelectrauma,[39,40] so HFOV is also believed to reduce the risk of air leak syndrome.[16,35,41,42] Ultimately, the use of HFOV has been determined to be an ideal lung-protective ventilator strategy.[39] There have been various studies that indicate that HFOV can reduce VILI compared with CMV using conventional ventilator strategies (nonprotective ventilation strategies), and even when CMV is used with a protective ventilation strategy.[39]

Analyzing the clinical role of HFOV on air leak syndrome, the results did not completely support the proposed beneficial effects. In treating premature infants with RDS, HFOV has also been used as elective or rescue therapies. A meta-analysis involving 10 trials (3229 participants) by Cools et al demonstrated that elective HFOV did not decrease the incidence of gross (RR 1.08, 95%CI 0.88−1.32) or any pulmonary leak (RR 1.15, 95%CI 1.00−1.33) in premature infants with RDS.[43] In addition, Cools et al published a systemic review on elective HFOV therapy in premature infants involving 17 eligible studies (3652 infants), all with publication dates between 1989 and 2008.[44] Among them, 12 trials (2766 infants) reported data showing any pulmonary air leaks and revealed a small but significant increase in the HFOV group (RR 1.19, 95%CI 1.05−1.34; Table 3).[38,44−64] In addition, 10 trials (1829 infants) revealed a non-significant trend toward an increase in HFOV group (RR 1.30, 95%CI 0.99−1.70]) in the analysis of gross pulmonary air leak (pneumomediastinum or pneumothorax; Table 3).[44] The limitations of this review were that the HFOV ventilators and the results among trials were quite variable. Furthermore, no clear overall benefit or harm resulting from HFOV was demonstrated by these clinical trials.

In the systemic review of rescue HFOV therapy in premature infants with severe respiratory dysfunction by Bhuta and Henderson-Smartb, only one randomized controlled trial of 182 infants was chosen,[47] and that was published in 1993 by the HIFO study group.[48] This single trial demonstrated that any new pulmonary air leak was significantly reduced in HFOV treated infants than the use of CMV (RR 0.73, 95%CI 0.55−0.96; Table 3), but there was no significant difference in the rate of PIE or of gross pulmonary air leak (RR 0.80, 95% CI 0.45−1.42; Table 3).[44,48] However, the limitation of this review is that only one trial was undertaken, and that the majority of enrolled infants were not treated with exogenous surfactant.

A recent systemic review of full-term or near-term infants (born at 35 weeks gestational age or more) with severe respiratory failure done by Henderson-Smart et al included 2 clinical trials published in 1994 (79 infants, rescue therapy) and 2005 (118 infants, elective therapy; Table 3).[38] Neither study described any significant difference in the risk of air leaks between HFOV and CMV.[38]

Therefore, there is lack of evidence to support the routine use of HFOV instead of CMV to reduce air leaks in newborn infants with acute pulmonary dysfunction. Further trials on more risky newborn infants, and comparing the different therapeutic strategies for HFOV and CMV may be necessary for future clinical application.

3.2.2. HFJV

The HFJV procedure requires use of a special endotracheal tube with a side lumen to deliver the jet ventilations (240−660

Table 3
Summary of the relative risk (RR) of pulmonary air leak in published data (HFOV vs. CMV).

Author/year[(Reference)]	Air leak	HFOV *n/N* (%)	CMV *n/N* (%)	RR [95% CI]	HFOV ventilator type
At or near term					
Rescue					
Clark 1994[38,46]	AAL	4/39 (10)	6/40 (15)	0.68 [0.21–2.24]	B
Elective					
Rojas 2005[38,45]	AAL	2/54 (4)	1/64 (2)	2.37 [0.22–25.43]	B
Preterm					
Rescue					
HIFO 1993[47,48]	AAL	39/83 (47)	56/87 (64)	0.73 [0.55–0.96][a]	B
	GAL	16/83 (19)	21/87 (24)	0.80 [0.45–1.42]	B
Elective					
HIFI 1989[44,49]	AAL	148/327 (45)	131/346 (38)	1.20 [1.00–1.43]	A
Clark 1992[44,50]	AAL	18/37 (49)	10/28 (36)	1.36 [0.75–2.47]	B
	GAL	14/37 (38)	8/28 (29)	1.32 [0.65–2.71]	B
Ogawa 1993[44,51]	AAL	4/46 (9)	6/46 (13)	0.67 [0.20–2.21]	A
Gerstman 1996[44,52]	AAL	8/64 (12.5)	11/61 (18)	0.69 [0.30–1.61]	B
Rettwitz-Volk 1998[44,53]	AAL	7/46 (15.2)	7/50 (14)	1.09 [0.41–2.86]	G
	GAL	3/46 (7)	5/50 (10)	0.65 [0.17–2.58]	G
Thome 1998[44,54]	AAL	59/140 (42)	44/144 (31)	1.38 [1.01–1.89][a]	C
	GAL	20/140 (14)	11/144 (8)	1.87 [0.93–3.76]	C
Plavka 1999[44,55]	AAL	3/21 (14)	3/20 (15)	0.95 [0.22–4.18]	B
	GAL	1/21 (5)	2/20 (10)	0.48 [0.05–4.85]	B
Moriette 2001[44,56]	GAL	7/139 (5)	4/134 (3)	1.69 [0.51–5.63]	D
Courtney 2002[44,57]	GAL	32/244 (13)	35/254 (14)	1.01 [0.64–1.59]	B
Johnson 2002[44,58]	AAL	64/400 (16)	72/397 (18)	0.88 [0.65–1.20]	B,E,F
Craft 2003[44,59]	AAL	8/22 (36)	6/24 (25)	1.45 [0.60–3.53]	C
Schreiber 2003[44,60]	AAL	47/102 (46)	29/105 (28)	1.67 [1.15–2.43][a]	B
	GAL	17/102 (17)	10/105 (10)	1.75 [0.84–3.64]	B
Van Reempts 2003[44,61]	AAL	24/147 (16)	16/153 (10)	1.56 [0.86–2.82]	B,C
	GAL	11/147 (7)	7/153 (5)	1.64 [0.65–4.10]	B,C
Vento 2005[44,62]	GAL	2/20 (10)	1/20 (5)	2.00 [0.20–20.33]	F
Dani 2006[44,63]	GAL	0/13 (0)	1/12 (8)	0.31 [0.01–6.94]	B
Lista 2008[44,64]	AAL	1/19 (5)	1/21 (5)	1.11 [0.07–16.47]	F
Sum of AAL (12 trials)[44]	AAL	391/1371 (29)	336/1395 (24)	1.19 [1.05–1.34][a]	
Sum of GAL (10 trials)[44]	GAL	107/909 (12)	82/920 (9)	1.30 [0.99–1.70]	

AAL = any air leak; GAL = gross air leak (excluding pulmonary interstitial emphysema alone); CMV = conventional mechanical ventilation; HFOV = high-frequency oscillatory ventilation.
HFOV ventilator: A = Hummingbird; B = SensorMedics 3100A; C = Infant Star; D = Dufour-OHF1; E = SLE-2000HFO; F = Dräger Babylog 8000; G = Stephan SHF3000 piston oscillator.
[a] Presence of significant difference ($p < 0.05$) between HFOV and CMV group.

breaths/min), which are superimposed on a background gas flow from a conventional ventilator. So, CMV can be delivered in conjunction with HFJV.[65–67] The exhalation phases are passive, and the major difference between HFJV and HFOV is the inspiratory to expiratory ratios (I/E). The I/E in HFOV may be fixed at 1:1 or adjustable on the inspiratory percentage (usually 33%); in HFJV, the I/E is usually set at 1:6. Theoretically, the very low I/E makes it effective in managing patients with PIE.[65,66]

In 1991, Keszler et al reported that HFJV could result in improved ventilation at lower peak and mean airway pressures, and more rapid radiographic improvement of PIE in neonatal infants than CMV.[65] This study was also the only study (144 infants) included in the meta-analysis of Cochrane database systemic review in 2006 for rescue use of HFJV in preterm infants.[66] However, there was no significant difference between CMV and HFJV in the outcome analysis of new air leaks. In an earlier meta-analysis of elective HFJV use for RDS in 248 preterm infants in 2000, three trials were included, but there was also no significant difference between HFJV and CMV in the outcome analysis of air leaks.[67]

In conclusion, neonatal air leak syndrome may be asymptomatic, or present as an emergency that requires the attention of trained care providers available in neonatal intensive care units on a continuing basis. To reduce the risk of air leak syndrome, gentle ventilations are the key to caring for mechanically ventilated infants. The role that HFOV and HFJV may play in preventing new air leaks in newborn infants remains unsettled due to a lack of dispositive evidence, so further investigation is necessary to best ascertain future clinical applications.

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