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PATHOGENESIS, PATHOLOGY AND PATHOPHYSIOLOGY OF PULMONARY SEQUELAE OF BRONCHOPULMONARY DYSPLASIA IN PREMATURE INFANTS

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1. ABSTRACT

The incidence of bronchopulmonary dysplasia (BPD), defined as oxygen need at 36 weeks of postmenstrual age, is about 30% for infants with birth weights <1000 grams and is now infrequent in infants with >1200 grams birth weight and >30weeks gestation. The pathogenesis of BPD is multifactorial, with cytokines appearing to play a key role in initiation, propagation and resolution of this process. The pathology of BPD seen in the pre-surfactant era was remarkable for the presence of airway injury, inflammation and parenchymal fibrosis**;** pathology of "new" BPD reveals more uniform inflation and less marked fibrosis with both small and large airways being free of epithelial metaplasia, smooth muscle hypertrophy and fibrosis. There is, however, an arrest in acinar development.

Up to 50% of infants with BPD require readmission to the hospital for lower respiratory tract illness in the first year of life. There are significant effects on lung mechanics, gas exchange and pulmonary vasculature**.** Pulmonary outcome in BPD include normalization of pulmonary mechanics and lung volumes over time as somatic and lung growth occurs whereas abnormality of the small airway persists. Airway hyper-responsiveness has been reported in long-term survivors of BPD, with no decrease in exercise capacity. The majority of the radiological findings reveal persistence of mild to moderate abnormalities long term.

BPD is a result of dynamic processes involving inflammation, injury, repair and maturation. Infants with BPD have significant pulmonary sequelae during childhood and adolescence; whether the pulmonary dysfunction in these patients will predispose them to obstructive lung disease as older adults, remains to be seen.

2. INTRODUCTION

Bronchopulmonary Dysplasia (BPD) is characterized by tachypnea /wheezing and retractions with typical radiographic features of hyperinflation, increased linear densities and cystic areas as originally described by Northway in 1967 (1). "Classic" BPD was seen in preterm infants with severe Respiratory distress syndrome (RDS) who required high inspired oxygen concentrations and prolonged mechanical ventilation (2) and was characterized by early interstitial and alveolar edema, followed by persistent inflammation, fibrosis and small airway disease (3). It is believed that both oxygen and mechanical ventilation are responsible for the lung injury (3). With the increasing survival of extremely premature infants, "classic BPD" has been superseded by the "new" BPD (4). Clinical and epidemiological data strongly suggest that infections, either prenatal or nosocomial, and the presence of patent ductus arteriosus (PDA) play a major role in the development of this new BPD (4). Besides the 2 above described forms, other atypical forms of BPD have also been described (5).

Table 1. Diagnostic criteria for BPD [1]

	MILD Supplemental O_2 (for 28 days) and	**MODERATE Supplemental O_2 (for 28 days) and**	**SEVERE Supplemental O_2 (for 28 days) and**
< 32 weeks GA at birth	RA at 36 weeks corrected GA or at discharge	<0.3 FiO_2 at 36 weeks corrected GA or at discharge	≥ 0.3 FiO_2 +/- positive pressure support at 36 weeks corrected GA or at discharge
≥ 32 weeks GA at birth	RA by postnatal day 56 or at discharge	<0.3 FiO_2 by postnatal day 56 or at discharge	≥ 0.3 FiO_2 +/- positive pressure support by postnatal day 56 or at discharge

[1] Adapted from ref. 11. BPD: bronchopulmonary dysplasia; FiO_2: fraction of inspired oxygen; GA: gestational age; RA: room air

Table 2. Incidence of BPD [1]

Birth weight (grams)	**BPD [2]**	**BPD [3]**
< 750	90-100%	52-54%
750-999	50-70%	33-34%
1000-1249	30-60%	15-20%
1250-1499	6-40%	7-10%

[1] Adapted from ref. 105. Data from refs. [2] 106, 107, 2 Supplemental O_2 at 28 days; [3] Supplemental O_2 at 36 weeks corrected gestational ag.

Long term survivors of BPD tend to be a heterogeneous population as continuing injury, inflammation, healing, repair, growth, and maturation occur concurrently or sequentially in the lung (6). Since the definition of BPD is variable (see below) and management of the premature newborn has been evolving over time, it is expected that the spectrum of pulmonary abnormalities and outcomes will be heterogeneous (6).

The present review will focus on the pathogenesis, pathology and pathophysiology of the pulmonary sequelae of BPD.

3. DEFINITION

There is no universally accepted definition of BPD. Bancalari and his associates (7) defined the infant with BPD as one requiring more than 3 days of positive pressure ventilation in the first week of life and having clinical symptoms of respiratory distress requiring supplemental oxygen. The Bureau of Maternal and Child Health (8) put forward the following diagnostic criterion:

1. Positive pressure ventilation during the first 2 days of life, for a minimum of 3 days.
2. Clinical signs of respiratory compromise persisting longer than 28 days.
3. Requirements for supplemental oxygen longer than 28 days of age to maintain partial pressures of arterial oxygen (Pa O_2) of
   >50 mm of Hg.
4. Chest radiograph with findings characteristic of BPD.

Other definitions include supplemental O_2 at 28 days of age (1), need for O_2 at 28 days with at least 21 days of O_2 supplementation and a consistent chest X-ray (9), and O_2 need at 36 weeks corrected gestational age (10). A recent consensus meeting suggested reverting to the previous nomenclature of BPD rather than chronic lung disease of infancy since it is clearly distinct from the multiple chronic lung diseases of later life (11). New criteria for diagnosis of BPD and its severity were also proposed (11). These have been summarized in Table 1.

4. INCIDENCE

The exact incidence of BPD is difficult to assess since there is no universally accepted definition; however, the reported incidence varies from 12-70%, and is inversely related to birth-weight (1). The "classic" BPD as first described by Northway has now been replaced by less severe forms which are primarily observed in very small premature children (12-14). The incidence of BPD, defined as oxygen need at 36 weeks of postmenstrual age, is about 30% for infants with birth weights <1000 grams. BPD is now thought to be infrequent in infants with >1200 grams birth weight and >30weeks gestation (15). See Table 2.

The incidence of pulmonary morbidity in BPD is significantly high. At a mean age of assessment of 5.4 years, children with BPD had a significantly higher risk of developing asthma than the general population (16). At age 14, the rate of readmission to the hospital for pneumonia or asthma (in the previous year) was 5% (2/42) in infants (<1501 g birth weight) with BPD vs. 0% (0/138) in infants without BPD; 19% of infants with BPD had asthma as compared to 18% without BPD (17).

5. PATHOGENESIS

"Classic" BPD is thought to result from an acute insult to the neonatal lung following therapy with high concentrations of oxygen and mechanical ventilation with high positive pressures (3,4). Research in pre-term baboons and sheep have revealed that high concentrations of oxygen and positive pressure ventilation results in cellular injury to the immature lung and results in impairment or inhibition of lung alveolar and vascular development (18). Direct cellular injury occurs from

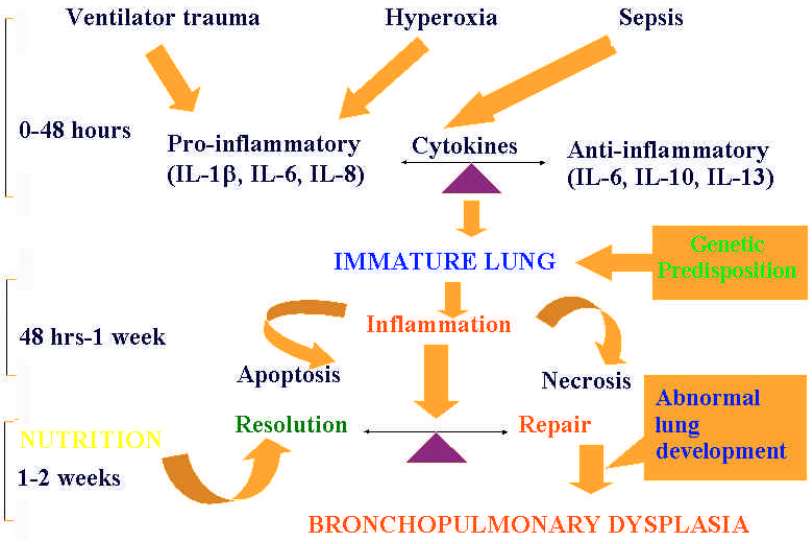

Figure 1. Pathogenesis of BPD. For text for details.

oxygen radicals that are not detoxified by antioxidant defense system of the immature host.

With the increasing practice of administration of antenatal steroids and use of exogenous surfactant, premature babies have decreased severity of RDS (4). On the other hand, extremely preterm babies with more immature lungs are being saved. These babies, over time, develop gradually increasing need for supplemental oxygen and dependence on mechanical ventilation (4).

The pathogenesis of BPD, as described above, is multifactorial with inflammation playing a key role. A proposed sequence of events has been depicted in Figure 1. Sepsis *in-utero* (locally in the lung or systemic), along with ventilator-induced trauma as well as hyperoxia initiates an inflammatory cascade, which acts on the immature lung. Cytokines appear to play a key role in the initiation, propagation and resolution of this process. Cytokines can be considered "pro-" while others are "anti-inflammatory". This distinction is not absolute, as the same cytokine either promote or antagonize inflammation at different instances (19). Depending on the degree of lung injury, the damage can resolve (heal) with growth, resulting in normal lung architecture. In others, repair of the lung injury occurs by fibrosis; thus resulting in typical pathological features of BPD where areas of normal lung architecture are interspersed with areas of abnormal lung. There appears to be a genetic component too, as infants with a similar degree of lung immaturity and exposure to "environmental factors" (such as oxygen, ventilation) may or may not develop BPD.

The role of intrauterine infection (20) and other factors implicated in the pathogenesis of BPD have been recently reviewed (3,4,21-24).

Various pro-inflammatory and chemotactic factors are present in the preterm ventilated lung. Markers of inflammation have also been found to be elevated in preterm infants with BPD; they have increased number of neuroendocrine cells (25), mast cells, and eosinophils in their lungs. Other factors, for example, macrophages, Interleukin (IL)-6, IL-8 and macrophage protein 1 are increased in the airspaces and anti-inflammatory cytokines such as IL-10 are decreased (26-34). Though the increase in granulocytes in the preterm lung has been demonstrated, and is thought to propagate ongoing lung injury, the exact mechanism of how this occurs and its role in progression of lung injury is still unclear (19, 35). Inflammation interferes with normal anatomic development of airway and alveoli and abnormal healing in the premature infant due to immaturity further exacerbates lung tissue damage (19, 35-37).

Different outcomes reported in infants matched for gestation, duration of mechanical ventilation and nutritional status, also suggest a genetic risk for development for respiratory distress (38). Genetic factors including race, gender, and family history of airway hyper-responsiveness have also been found to play a role in development of BPD. Genetic polymorphisms in the population may result in increased risk of developing BPD as shown for RDS in the Finnish population (39). Another factor that has been found to indirectly affect development of BPD is malnutrition, since it may result in decreased ability to resist damage and repair. Recurrent viral and bacterial infections causing alveolitis may also cause ongoing damage and increase in respiratory morbidity (40).

6. PATHOLOGY

Pathology of the BPD lung from the pre-surfactant era was remarkable for presence of airway injury, airway inflammation and parenchymal fibrosis. Rosan described four pathological stages of BPD (41). Stage 1: Interstitial and intra-alveolar edema followed by

early necrosis of the lung lining cells. Stage 2: The foregoing plus varying degrees of cellular repair that resulted in thinning and attentuation of the residual lung lining cells as they attempted to spread across the necrotic surfaces. Stage 3: Persistent fetal arterioles; metaplastic, bizarre or dysplastic mucosal cells with prominent bronchiolar musculature; irregular pulmonary aeration with pneumatoceles. Stage 4: Inappropriate regeneration and repair in which the entire lung was hyper-expanded.

Stocker (42) has reported on pathological features of long-standing "healed" BPD in 28, three to forty month old infants who had moderate to severe BPD in the neonatal period. The cause of death in 68% of these infants was progressive respiratory failure related to residual pulmonary effects. He reported that the single most consistent residual finding in these infants was alveolar septal fibrosis; the extent of this alveolar septal fibrosis was strikingly variable, with moderate to severe fibrosis in one area and normally inflated and or hyper-inflated lung in the adjacent sub-lobule or lobe. He further speculated that this variability may be related to a protective effect of necrotizing bronchiolitis, commonly seen in acute stages of BPD, whereby the occlusion of bronchioles may shield the distal sub-lobule from the high oxygen tension and ventilatory pressures.

Recent data reveals "new" pathological findings in lungs of infants dying with BPD. There is more uniform inflation and less marked fibrosis and both small and large airways are free of epithelial metaplasia, smooth muscle hypertrophy and fibrosis, as compared to lungs of infants that did not receive surfactant, and arrest in acinar development, which was observed in both the lungs of the surfactant treated as well as untreated patients (43). In preterm baboons that were mechanically ventilated and developed BPD, a permanent decrease in the number of alveoli was observed although the airspaces were found to be enlarged, resulting in decreased total internal surface area in BPD survivors (44). Along with decreased alveolar number, a decrease in the arterial count has also been reported such that the alveolar/arterial ratio remained normal in infants with chronic lung disease (45).

Bhatt *et al* (46) have shown that infants with BPD have dysmorphic pulmonary microvasculature with decreased vessel growth, dilated vessels deep within the thickened septae and decreased vessel network formation. Infants with BPD also have a reduced vascular endothelial growth factor (VEGF) mRNA and protein expression, and decrease in the receptor for the growth factor Flt-1 (VEGFR-1). There was decreased expression of other endothelial markers, platelet endothelial cell adhesion molecule (PECAM-1) and the receptor for angiopoietin 1, TIE-2, suggesting disruption of the alveolar vasculature and that these abnormalities may have resulted from disordered expression of angiogenic growth factors and their receptors. In term infants, staining for VEGF in the lung was seen in bronchial epithelial cells and in alveolar macrophages while in fetuses and premature infants, it was detected in bronchial epithelial cells, alveolar epithelial cuboidal cells, endothelial cells, and alveolar macrophages (47). In infants with BPD, staining was seen in bronchial epithelial cells and alveolar macrophages, vascular endothelium, and in Type II pneumocytes (47). In fetuses, endothelial cells, intima of the small arteries, as well as bronchial and alveolar epithelium were strongly positive for Flt-1. In premature infants, a similar staining reaction was seen in vessels and bronchi. In term infants, positive staining was visible in the endothelium, the intima of the small arteries, and in bronchial epithelial cells. In infants with BPD, a positive staining reaction was visible throughout the walls of small arteries, and in the endothelial lining of veins and capillaries; bronchial epithelium was positive, as were Type II pneumocytes in the alveoli, and alveolar macrophages (47). VEGF and Flt-1 staining was seen in Type II pneumocytes in alveolar epithelium only in those infants with BPD. The presence of VEGF in the alveolar epithelium of infants with BPD may be associated with the healing process after RDS or play a role in the pathogenesis of BPD (47).

7. PULMONARY PATHOPHYSIOLOGY

7.1. Lung mechanics

Development of BPD results in significant alteration of lung mechanics. Pulmonary compliance is diminished by a combination of lung fibrosis, over-distension, increased airway resistance, and increase in lung water resulting from the disruption of the alveolar-capillary interface.

Decreased lung compliance and increased airway resistance because of fibrosis causes an increase in work of breathing, resulting in clinical findings of tachypnea, intercostal retractions and paradoxical breathing.

7.2. Pulmonary gas exchange

Areas of alveolar collapse that still have adequate perfusion cause ventilation/ perfusion mismatching which results in hypoxia. Areas of increased pulmonary vascular resistance may cause intrapulmonary shunting hence worsening hypoxia. Decreased compliance leads to increased work of breathing and increased production of CO_2 causing hypercarbia. Alveolar and airway damage also results in prolongation of alveolar time constants resulting both in air trapping, hypoventilation and hypercarbia.

7.3. Pulmonary hypertension

Pulmonary circulation has an important function in regulating gas exchange by maintaining adequate matching of perfusion with ventilation. Pulmonary arteries and veins develop in conjunction with the conducting airways and are in place by the pseudoglandular phase of the lung development but the formation of an extensive capillary network does not occur till the alveolar phase of maturation. The pulmonary bed is extremely sensitive to oxidant, pressure and inflammatory injury. Though the pathogenesis, pathophysiology and treatment of pulmonary hypertension is poorly understood, experimental models have demonstrated adverse effects of hyperoxia in the developing lung circulation and the endothelial cells are known to be more prone to injury owing to the generation of oxygen radicals and such as superoxide anion, hydroxyl

anion and other radicals. Mechanical ventilation can cause significant vascular injury by causing epithelial injury because of repetitive shear stress. Pulmonary circulation may thus suffer substantial injury in the preterm lung. Pulmonary vascular disease in infants with BPD results from 1) interruption of the pulmonary vascular bed growth and development due to premature birth, 2) incomplete adaptation of lung circulation, 3) effects of acute lung injury, and 4) effects of lung repair and remodeling. Pulmonary hypertension causes significant mortality and morbidity in this patient population. Clinically, it contributes to recurrent cyanosis, pulmonary edema, and increased risk of death following lower respiratory tract infections for example, respiratory syncytial virus (RSV) and influenza (48-51). Earlier studies revealed 50% mortality in patients with BPD and echocardiographic findings of pulmonary hypertension. Others have also reported a high mortality and morbidity in infants with severe BPD and pulmonary hypertension (48,50,51).

Tomashefski *et al* (52) reported morphometric studies of 8 BPD patients who were less than 2 months of age at the time of death and revealed increased peripheral extension of smooth muscle to intra-acinar vessels, which were fully muscular. They also reported occasional thromboemboli, a tendency to decreased medial thickness of muscular arteries and a normal arterial count. Stocker (42) studied infants dying with "healed" BPD and found only mild pulmonary hypertensive changes in most infants despite a 70% incidence of right ventricular hypertrophy (RVH).

Fouran *et al* (53) obtained serial echocardiographs in 10 infants with severe BPD (2 months to 13 months of age); they found elevated right systolic time interval (RSTI) in all these infants and all these infants died during the duration of the study, suggesting that persistent elevation of RSTI at 3 months of age is a poor prognostic feature in infants with BPD. Melnick *et al* (54) found normal RSTI in infants with BPD; however, these infants had striking increases in left ventricular and septal dimensions suggesting presence of severe concentric left ventricular hypertrophy. Harrod *et al* (55) reported elevated pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) in 6 children with BPD on cardiac catheterization in a follow-up study. They found elevated PAP and PVR and reported no improvement on follow-up. A more recent study (56) studied serial pulmonary artery pressures in 54 premature babies with RDS by echocardiogram at birth and at one month. Of these infants, 63% developed BPD. The authors observed a drop in PAP over the first 14 days in all of these infants. The decline in pressures was lower in the group with BPD than the group that had no evidence of lung disease; furthermore, the PAP increased in the group with chronic lung disease over the next 14-28 days (56).

Serial echocardiograms and EKG are clinically useful for follow-up. Cardiac catheterization is not usually indicated but in exceptional situations may serve to quantitate the severity of pulmonary hypertension, help rule out anatomical cardiac lesions, structural abnormalities of the pulmonary vasculature, thromboemboli and define optimal levels of supplemental oxygen therapy. Berman *et al* (57) performed cardiac catheterization in infants with BPD (mean age 15 months) and reported normal left ventricular function, poor correlation of PVR and RSTI measured simultaneously, and normal findings on angiography. Three of 9 children studied (who had PaO_2 <50 mmHg) were responsive to supplemental O_2 while the other 6 were not; the investigators concluded that BPD patients demonstrate variable degrees of pulmonary hypertension but little oxygen responsiveness (57). On the other hand, the data from home oxygen therapy program revealed that although 10 out 23 infants had RVH at discharge from the nursery, only 3 showed persistent RVH at follow-up, suggesting that, with avoidance of hypoxia, infants with BPD may be capable of resolving clinical symptoms of pulmonary hypertension over time (58). In the longest follow-up study in patients with BPD reported to date (59), where a group of adolescents and young adults were studied (mean age 18.7 years), none of the subjects had pulmonary hypertension and only one presented with RVH.

8. PULMONARY OUTCOME IN BPD

8.1. Respiratory Morbidity

The literature regarding outcomes in BPD is difficult to interpret due to lack of a generally accepted definition of BPD, varying patient population, patient attrition, and poor predictive value of short-term outcome studies. Furman *et al* (60) studied rates of hospitalizations in children with BPD. In their study, 50% of the 124 very low birth weight (VLBW) infants with severe chronic lung disease studied were re-hospitalized in the first year of life and 36% were hospitalized in the second year of life. The commonest reasons for re-hospitalization in this population were reactive airway disease (11%), pneumonia (14%), RSV infection (7%), and worsening BPD (5%); duration of neonatal stay in the hospital and the total hospital stay during the first year were associated with all measures of chronic lung disease severity whereas the duration of re-hospitalization was associated only with duration of oxygen dependence. After 4-5 years of life, hospitalizations for respiratory problems decrease (61-64). Northway *et al* (59) followed 23 survivors of BPD (mean age 18.7) and reported that 25% of adolescents with BPD had significant pulmonary symptoms (higher number of wheezing episodes, pneumonias and long term medications), when compared to two different age matched control groups, one with similar birth weights and gestation that did not undergo mechanical ventilation and the second, normal non-smoking young adults and adolescents born full term. Another follow-up study (65) of lung function and respiratory symptoms in children (aged 8-18 years) revealed no differences in respiratory symptoms in the BPD group when compared to age matched normal controls, children with RDS but no BPD, and preterms with no lung disease; though, they found increased airway responsiveness and significantly decreased forced expiratory volume in the first second (FEV_1) in the BPD group.

8.2. Pulmonary function

Changes in pulmonary function occur with growth in infants with BPD; normalization of pulmonary mechanics and lung volumes occurs over time whereas abnormality of the small airway persists, suggesting that the processes for lung parenchymal repair may differ from those affecting the conducting airways. The conducting airways are completely formed by 17 weeks of gestation, whereas majority of alveolarization occurs post-natally, so that with growth the "new" alveoli may indeed replace the "damaged" alveoli. Even though the conducting airway increases in size and caliber, the "damaged" airway persists, resulting in dysnaptic growth. This is in concordance with findings of decreased flow rates at rest, and normal functional residual capacity (FRC) and total lung capacity (TLC) and increased ratio of residual volume to TLC (RV/TLC) on pulmonary function testing of children with history of BPD, when compared with normal full term children, preterms without BPD and children with history of RDS.

Pulmonary function tests (PFT) in infants with BPD showed low maximum flow rates at functional residual capacity (Vmax FRC) when compared to full term and preterm controls (66-68). Farstad *et al* (69) demonstrated that infants with BPD had lower Vmax FRC at 1 and 2 years of age when compared with preterm children with history of mild and moderate RDS alone. Decreased airway conductance has also been demonstrated in this population up to 3 years of age when compared with full term and preterm controls (70). A follow-up study revealed history of recurrent wheeze, increased incidence of chest wall deformities, significantly lower forced vital capacity (FVC), FEV_1, forced expiratory flow at 25% of FVC ($FEF_{25-75\%}$), RV/TLC and evidence of obstructive lung disease in adolescents and adults with history of BPD when compared to normal full term infants and preterm controls without BPD (59). Gross *et al* evaluated 125 children at 7 years of age and reported decreased FVC, FEV_1 and $FEF_{25-75\%}$ and an increased bronchial responsiveness in children with history of BPD when compared to socio-demographically matched normal controls (62). Mallory *et al* (71), also demonstrated significant improvement in lung volumes over the first 3 years of life in 11 patients with severe BPD, but here again there was persistence of small airway obstruction with maximum expiratory flows at 25% of FVC being as low as 10% of the predicted values in their most severe patients. Blayney *et al* (72) studied 32 patients with BPD at age 7 and 10 years and found that children with the most significant degree of airway obstruction at 7 years improved by age 10 and children with normal pulmonary functions at 7 years of age continued to remain normal at age 10, indicating continuing lung growth and improvement in lung functions during late childhood. Koumbourlis *et al* (73) studied serial lung functions in children 8-15 years of age over an 8-year period; they too found normal FEV_1 and peak flows, normalization of lung volumes overtime and persistent small airway obstruction. Talmaciu *et al* (74) compared normoxic infants with BPD who were 24 months and older, to age-matched infants with BPD who had a persistent need for supplemental oxygen, and found abnormal pulmonary mechanics in all children with BPD, but little correlation between degree of abnormalities in pulmonary function and prolonged need for supplemental oxygen.

In patients with RDS with no BPD, some studies reveal normal lung function (75-78). Others have reported airway obstruction and air trapping (61,79-84). Reduced airflow has been reported in preterms with no evidence of lung disease in the neonatal period, bringing forth the argument that prematurity itself may predispose to dysynaptic airway growth irrespective of any neonatal lung disease.

8.3. Airway disease

Airway hyper-repsonsiveness has been reported in long-term survivors of BPD (59,65,73,85-88). It is unclear if BPD is caused by lung injury sustained in the neonatal period and whether genetic predisposition plays a role in its development. Evidence of airway reactivity in premature infants has been demonstrated as early as 12 days of age and a highly significant correlation between the degree of airway reactivity and the severity of respiratory disease, as determined by the duration of ventilator dependence has been shown, suggesting that airway reactivity may play an important role in the development and severity of BPD (89). No increase in prevalence of atopy has been found in children with BPD (59) and bronchial hyper-responsiveness was reported to be unrelated to atopic status (79). The role of maternal asthma has not been defined in patients with BPD. Bertrand *et al* studied ex-premature infants at 7-12 years of age and showed an increased prevalence of bronchial hyper-responsiveness (whether or not they had RDS) as well as an increase in bronchial hyper-responsiveness in their sibling controls and their mothers postulating a link between premature labor and familial bronchial hyper-responsiveness (80). Kelly *et al* have also shown that maternal asthma is a risk factor for development of preterm delivery (90) while others have shown no increase in the prevalence of maternal asthma, family history of asthma or maternal airway hyper-responsiveness (59,61,79,83,88,91).

Although BPD affects primarily the small airways, large airway disease occurs commonly in this patient population. Tracheomalacia and bronchomalacia secondary to endotracheal intubation and prolonged mechanical ventilation is well known. Increase in central airway compliance may result in so called "BPD spells" which are acute cyanotic events most commonly seen in the older infants with BPD (92,93). Other airway problems include inspissated secretions, formation of granulation tissue and pseudopolyps (92).

Infants who develop chronic lung disease in the present era are probably born more immature than the ones studied in the past and the prognosis of this population may not be similar to that reported in the literature thus far. Hence the current survivors of BPD who reach adolescence and adulthood might become a new population calling for special preventive and therapeutic measures (6,94). Given the normal decline in FEV_1 with aging, young adults with

airway hyperreactivity and reduced flow rates due to BPD remain at a higher risk of developing severe obstructive disease as they age (6,94,95).

8.4. Exercise testing

Though the majority of survivors of BPD participate in play, exercise and other physical activities without symptoms, there is concern over their respiratory reserve given their often stormy perinatal period. Mitchell *et al* (96) studied carbon monoxide (CO) and acetylene (C_2H_2) gas transfer during exercise in school aged children (6-9 years) with past history of BPD and found decreases in soluble gas transfer in patients with BPD when compared with normal children born at full term as well as preterm children with no BPD; the authors concluded that this finding may be related to long term lung structural abnormality or residual right ventricular dysfunction. Santuz *et al* studied 12 children between the ages of 6-12 years with mild BPD and found decreased maximal exercise capacity (97); however, other studies done so far (79,88,98,99) show no reduction in exercise capacity in children with BPD when compared to children with healthy term infants or preterm babies without lung disease. Coates and his group evaluated their maximal exercise in 15 children with BPD between the ages of 7-14 years and found that though there was no decrease in maximum work load (W max) there was an increase in the respiratory rate and wasted ventilation in the BPD group, suggesting decreased respiratory reserve (100).

At this time, most of the data suggests that there is no decrease in exercise capacity in survivors of BPD though there is a concern about decreased respiratory reserve.

8.5. Radiological findings

There have been few follow-up studies that have looked at the long-term changes in radiological findings of BPD. Northway *et al* (59) found generally subtle radiological findings in survivors of BPD (mean age 18.7 yrs) including hyperinflation, interstitial and pleural thickening, blebs and peribronchial cuffing. Hakulinen *et al* (101) studied 10 patients with BPD on follow-up (6-9 yrs), compared them to normal full terms and preterms without BPD and found only minor fibrotic changes on chest radiographs in 40% of the BPD children. Andreasson *et al* studied 11 children with BPD at 8-10 years and compared them to age matched preterm infants with no BPD and found that 80% of the children with BPD had abnormal findings on chest radiographs (79). Children that had abnormal radiographs initially after being ventilated had a greater incidence of having abnormal findings on follow-up (79). Radiological findings continued to improve in children who had been studied in the prior 4 years (79).

High resolution computed tomography (CT) scan features in adult survivors of BPD included multifocal areas of reduced lung attenuation and perfusion, bronchial wall thickening, and decreased bronchus-to-pulmonary artery diameter ratios (102). Aquino *et al* (103) also reported high resolution CT findings in 26 older children with BPD. These reveal that 92% of these children had abnormal findings of which 85% had reticular opacities, 69% have areas of architectural distortion and 92% had gas trapping. There was a positive correlation between abnormal radiological findings and increased air trapping and obstructive lung disease on pulmonary function testing. Oppenheim *et al* (104) studied twenty-three children (mean age, 4 years) with BPD and those who had signs of chronic pulmonary dysfunction (recurrent episodes of coughing, wheezing, dyspnea, pneumonia, respiratory insufficiency) were examined with chest radiographs and high-resolution CT scans of the chest. They found that the chest radiographs showed hyper-expansion in 17, hyperlucent areas in 11, and linear opacities in 10 of the 23 children. Pleural thickening was not observed, and four children had normal findings on chest radiographs. All 23 CT scans showed abnormalities, including multifocal areas of hyperaeration, well-defined linear opacities, and triangular sub-pleural opacities with an external base and an internal apex. In 20 of 23 children, all three abnormalities were present and in 3 other children, two of these three abnormalities were found. The author concluded that lesions in survivors of BPD with chronic pulmonary dysfunction are visualized better on CT scans than on chest radiographs (104).

9. CONCLUSIONS

BPD is a result of dynamic processes involving inflammation, injury, repair and maturation. Outcomes of BPD are difficult to assess given the lack of a uniform definition, and changing modalities of management, including modes of ventilation. Infants with BPD have significant pulmonary sequelae during childhood and adolescence. Since there is progressive decrease in FEV_1 with aging in normal adults, whether the pulmonary dysfunction in these patients will predispose them to obstructive lung disease as older adults remains to be seen. Prevention of BPD starts at successful prevention of preterm deliveries; failing this, a better understanding of the effects of prenatal and postnatal factors on the immature lung is paramount to decreasing BPD.

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