

Bronchopulmonary dysplasia: an old and new disease

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The role of the clinical pathological dialogue in problem solving

Guest Editors: Gavino Faa, Vassilios Fanos, Peter Van Eyken

Abstract

Bronchopulmonary dysplasia (BPD) is one of the most common and significant medical complications associated with prematurity. It is made more serious by its morbidity and mortality rates. Although recent advances in clinical practice (prenatal steroids, surfactants, new ventilatory strategies, nutritional support) have contributed to improving the clinical course and outcomes of neonates with BPD, its overall incidence has not changed in the last decade owing to a concomitant increase in survival of prematures. The incidence of BPD is in fact inversely proportional to birth weight: 30% for neonates weighing less than 1,000 g, with different percentages in the single centres depending on clinical management and the ventilation criteria applied. However, to date, BPD represents not only a chronic pulmonary pathology in infancy that prevalently affects premature neonates who undergo mechanical ventilation and oxygen therapy for respiratory distress syndrome (RDS), but also prematures with minor signs of initial pulmonary pathology or term neonates requiring aggressive ventilatory support due to an acute and severe lung pathology.

Keywords

Bronchopulmonary dysplasia, prematurity, clinical aspects, prevention, therapy.

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Introduction

Despite the stronger association of bronchopulmonary dysplasia (BPD) and prematurity, genetic and epigenetic susceptibility (with involvement of growth factors and intracellular signal pathways) and environmental factors or those acquired in the prenatal and postnatal periods (hypoxia, hyperoxia, hemodynamic stress, infection, inflammation) also play a key role in the multifactorial pathogenesis of BPD which, through complex alterations, cause an altered growth of lung vascular and alveolar structures [1, 2].

High concentrations of cytokines produced in inflammatory settings (chorioamnionitis, postnatal infection, ventilation-induced pulmonary inflammation) are able both to modulate acute pulmonary injury and to exacerbate ventilation-induced pulmonary injury and alter the host's defences, with significant alterations of important signal pathways of cells involved in bronchial morphogenesis. Interleukin 1 β (IL1) and the transforming growth factor β 1 (TGF β 1) have been demonstrated to activate the kappa B nuclear factor (NF-kB) promoting pro-inflammatory cytokine capable of modulating normal expression of the pulmonary mesenchyme of the growth factor of fibroblasts 10 (FGF-10), responsible for the proper ramification of the airways and the bronchial tree.

Pro-inflammatory cytokines may also be produced in the context of a ventilation-induced pulmonary injury, with alterations in genes modulating angiogenesis; the onset of BPD secondary to volutrauma is also suggested in part by an inverse correlation between low levels of PaCO₂ and the risk of developing BPD [3].

Furthermore, oxidative stress may be the final common endpoint for a complex convergence of events, some genetically determined and some triggered by in utero stressors. The coexistence of inflammatory and oxidative lesions play an important role in determining BPD [4].

Although the role of colonization of *U. urealyticum* (an organism more frequently associated with chorioamnionitis and preterm birth) in the pathogenesis of BPD is controversial, experimental evidence has shown that prenatal exposure to

species of ureaplasma capable of causing disorders in pulmonary alveolarization in preterm lambs and that ureaplasma colonization of the trachea in preterm neonates may act synergically with ventilation-induced pulmonary injury in increasing the risk of BPD [5].

Recently, preeclampsia by itself has been defined as a risk factor for the consequent onset of BPD since it is responsible for an altered production of the protein (used as an early marker in the diagnosis of preeclampsia) tyrosine kinase 1 soluble (sFlt-1), having a pro-angiogenic effect with activity antagonistic to the growth factor of the vascular endothelium growth factor (VEGF) and to placental growth factor (PlGF). The altered cell signal mediated by VEGF (lower in concentration in aspired tracheal samples in prematures who later developed BPD) may contribute to the hyperoxia-induced vascular disorder (typical of BPD but also of retinopathy of prematurity) and to altered pulmonary alveolarization [1].

Other risk factors of BPD are represented by exposure to postnatal hypoxia (for pulmonary injury induced by an increased production of toxic radicals of oxygen capable of overcoming the host's normal defence mechanisms), by the excessive intake of fluids in the first days of life and by the perviousness of the ductus arteriosus (PDA) symptomatic of secondary pulmonary oedema with a left-right shunt (especially if sepsis and RDS coexist, with irreversible injury even in the context of an aggressive medical and surgical treatment for correction of the PDA).

Finally, a role in the pathogenesis of BPD appears to be played by genetic polymorphisms of receptor proteins, growth factors, surfactant proteins and mesenchymal and vascular progenitor cells [1].

Clinical aspects

Although BPD is defined as persistent oxygen dependency at 28 days of life, its traditional definition calls for the constant presence of respiratory signs and symptoms, of the need of oxygen dependence for treating hypoxemia and for radiological abnormalities at 36 weeks of post-conceptual life in neonates of gestational age (GA) below 32 weeks or 56 days of life in neonates with a higher GA [6].

The National Institute of Health (NIH) further classifies BPD as light, moderate or severe, depending on the oxygen required (none, less than 30% or above 30% and/or including noninvasive or invasive ventilatory support) to ensure normal oxygen saturation [6].

Although the incidence of BPD has been relatively stable, both its pathophysiology and clinical manifestations have changed greatly in the last twenty-five years.

The classic progressive stages of the old BPD with prominent fibroproliferation and acute pulmonary injury are now less representative and the “new” BPD often strikes prematures who need a minimum or no ventilatory support and/or require oxygen during the first days of life (normally in the first week) [7].

Ryan et al. have reported a predictive risk of BPD in the post-surfactant period in presence of oxygen dependence, peculiar radiological manifestations and the need for mechanical ventilation on the fourth day of life [8].

Histologically, new BPD is characterized by more regularly ventilated regions and less severe injury, but altered alveolar and vascular growth remains predominant (alteration in septation with alveoli larger and reduced in number and with a possible reduced pulmonary capillarity).

The “new” BPD of the surfactant era more frequently affects neonates of GA between 24 and 28 weeks, with a weight above or equal to 1,000 grams, with symptoms of RDS less serious and a lesser need of respiratory support [7].

Clinically, BPD presents with signs and symptoms of respiratory distress (respiratory work, persistent need of oxygen, episodes of apnoea-bradycardia, wheezing, prolonging of the expiratory phase at auscultation), while the radiological picture may more frequently show pulmonary hypoexpansion and diffuse cloudiness (especially at low GAs) or alternatively diffuse interstitial striae (correlatable with zones of fibrosis), irregular zones of atelectasis alternating with cystic areas, serious and diffuse pulmonary hyperexpansion and demineralization of the ribs caused by osteopenia of prematurity (a condition often associated with BPD).

The blood gas analysis often reveals hypercapnia (and consequent increase in bicarbonates) pH values, generally in compensation, especially in the chronic forms of BPD. The statistically significant association between hypercapnia in the first three days of life in prematures with a GA of less than 28 weeks of life and very severe BPD (independently of variables such as prematurity and mortality risk factors) loses its significance when considered in association with the duration of ventilation, thus reflecting a major predictive contribution of hypoxemia and hypercapnia to the risk of ventilation

and inflammation correlated with it, rather than a causal role of blood gas analysis alterations in the pathogenesis of BPD [9].

Electrolytic alterations (hyponatremia, hypokalemia, hypochloremia) may be found in the course of therapy with diuretics, while an increase of azotemia and creatinemia is often observed in the case of restriction of fluids [1].

Hematuria may be present in the case of nephrocalcinosis secondary to a prolonged use of diuretics, while the severe forms of BPD may associate with minor weight increase, pulmonary edema and hyperreactivity of the upper respiratory tract.

Neonates with BPD are also affected by a variable spectrum of pulmonary vascular disease (PVD), caused by the structural and functional involvement of lung circulation. The spectrum of such disorders may vary from clinically severe forms (such as pulmonary hypertension), to forms not diagnosed and thus their role in the long-term outcomes of BPD is underestimated [10].

In fact, although pulmonary hypertension represents an acknowledged component of new BPD capable of contributing significantly to the late morbidity and mortality (with a mortality rate that goes from 33% to 48% at two years from the diagnosis of pulmonary hypertension), PVD (through an increase in pulmonary vascular resistances and a reduced surface of gas exchange) may in the long run cause altered gas exchanges, a prolonged need of oxygen, intolerance to physical exercise and alteration in the distribution of pulmonary blood flow in response to acute respiratory infections, all conditions that often persist and become symptomatic even during infancy and adulthood [11].

Moreover, hemodynamic stress secondary to pulmonary hypertension has been suggested as being able to inhibit vascular and alveolar growth of the developing lung, as demonstrated in animal studies [11, 12].

It has also been demonstrated that in neonates with serious BPD the deoxygenated blood crosses the collateral intrapulmonary arteriovenous anastomotic vessels (normally closed in term neonates) prior to being oxygenated in the microcapillary bed, thus causing regional hypoxemia, which contributes to hypoxemic vasoconstriction and structural remodelling in those preterm neonates who develop pulmonary hypertension.

Pulmonary hypertension (**Fig. 1**) and the consequent hypertrophy of the right heart may

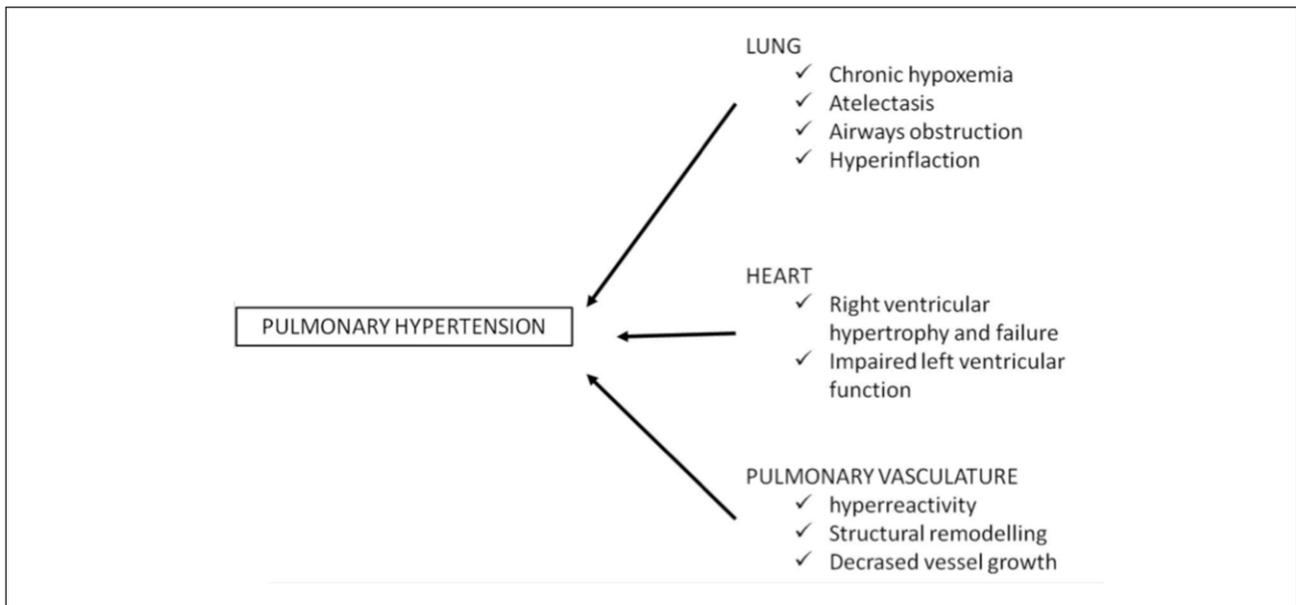


Figure 1. Factors that contribute to pulmonary hypertension in BPD.

over time lead to a picture of chronic heart and lung disease; in the case of right-sided heart decompensation there may also be hepatomegalia or abdominal dislocation of the liver secondary to pulmonary hyperexpansion [13, 14].

Prevention and therapy

Prenatal prophylaxis with corticosteroids in women at risk of preterm delivery has reduced the incidence of mortality and RDS by 50%, but not that of BPD; in the same way, the concomitant use of surfactant, although it reduces BPD mortality, has not in practice changed its incidence, but has increased survival of premature neonates [15].

At present, no therapy capable of preventing or reducing the effects of pro-inflammatory and anti-inflammatory cytokines on lung growth has been found.

Most controlled randomized trials performed to assess treatments for the prevention of BPD have failed to indicate an effective treatment, with the exception of inositol and clarithromycin (the latter for the prevention of infections sustained by ureaplasma species). However, these drugs have not been authorized by the Food and Drug Administration (FDA) and no meta-analyses have been performed [15].

To minimize pulmonary injury secondary to barotrauma-volutrauma, multiple respiratory and ventilatory strategies have been suggested

(for example: “gentle” ventilation modalities of pulmonary recruitment and permissive hypercapnia). In neonates in whom it is impossible to avoid intubation or who do not benefit from early administration of surfactant or noninvasive ventilation, such as nasal continuous positive airway pressure (nCPAP), target volume ventilation or rescue high-frequency oscillatory ventilation (HFOV) have been suggested in the case of patients with high ventilatory requirements. Target volume ventilation calls for the use of low tidal volumes (no more than 4-6 ml/kg) not only during the early stages of mechanical ventilation, but also during resuscitation in the delivery room. It represents a ventilatory strategy associated with a demonstrated reduction of pneumothorax, of days of ventilation, of hypocapnia, of production of interleukine 6 and 8 (secondary to ventilation-induced pulmonary injury) and combined risk of BPD and death [1, 2].

Moreover, the use of methylxanthine (caffeine), should be encouraged to reduce the incidence of episodes of apnoea and to facilitate interruption of mechanical ventilation.

Low concentrations of inspired oxygen should be used to avoid not only hypocapnia, volutrauma and oxygen toxicity (accentuated in preterms with a deficit of anti-oxidant defences) but also to prevent hypoxia-induced pulmonary hypertension. The optimal range of saturation has not been established and it is controversial whether it should exceed the 90-94% range [4].

Since a major incidence of pulmonary hypertension associated with BPD has been found in patients with more severe lung pathologies, any action capable of optimizing gas exchanges and avoiding intermittent hypoxemia is to be performed, even after hospitalization and at the patient's domicile.

Indeed, patients with serious forms of BPD have 30% of rehospitalisation, mostly for recurrent respiratory infections, and mortality for sepsis, respiratory infections or unexplained death in the first year of life.

Actions to be continued in BPD patients are: continuation of oxygen therapy or noninvasive ventilation at home, tracheostomy (in selected cases), prevention of hypoxia episodes, of aspiration and obstruction of the respiratory tract, prophylaxis of infections of the upper and lower airways such as respiratory syncytial virus prophylaxis with palivizumab, treatment of diseases having impact on gas exchanges (gastroesophageal reflux, tracheobronchomalacia).

Despite these preventive suggestions, patients who presented a moderate to severe form of BPD in adolescence may suffer from obstruction of the airways, bronchial hyperreactivity, hyperinflation. They also frequently present neurocognitive disabilities compared to those of the same age.

Adequate fluid support, therapy of symptomatic forms of PDA, increased calories and nutritional requirements (optimization of enteral nutrition, reduced use of vascular catheters for parenteral nutrition, concentrated formulas to prevent pulmonary edema) and supplementation with antioxidants, all represent other support strategies in the treatment of BPD patients [2].

The use of intramuscular vitamin A, with relative monitoring of hematic concentrations, in amounts sufficient to maintain the normal serum concentration of retinol, seems to reduce oxygen dependence at 36 weeks of postconceptional life, but does not modify the long-term neurological and pulmonary outcomes.

The use of diuretics (furosemide, bumetanide, the combined use of spironolactone and chlorothiazide) and bronchodilators (beta 2 agonists, anticholinergic agents and theophyllin) is not universally recommended and the effects, like those of vitamin A, would appear to be generally immediate and limited in time.

Nitric oxide (NO) is a vasodilator capable of reducing pulmonary vascular tone and preventing pulmonary inflammation associated with me-

chanical ventilation. Actually NO represents the priority treatment and provides major safety documented for neonates presenting pulmonary hypoplasia and severe hypoxemia associated with pulmonary hypertension. Assessments concerning its noninvasive use in prematures at risk of BPD and its effects in neonates with developing BPD (after the first week of life) are now in progress [16].

The use of vasodilators (**Tab. 1**) in the treatment of severe forms of pulmonary hypertension should be reserved to selected cases after excluding forms of venous pulmonary obstruction, dysfunction of the left ventricle, cardiac shunts and collateral systemic pulmonary circles. The FDA has recently expressly recommended not to use a selective inhibitor of 5 phosphodiesterase, Sildenafil, owing to increased dose-correlated mortality in patients treated for pulmonary hypertension secondary to idiopathic arterial pulmonary hypertension and congenital cardiopathy, in patients from 1 to 17 years of age, but no opinion has been expressed for babies below the age of one year, for whom its use remains off-label [13].

A meta-analysis of randomized studies has demonstrated that systemic corticosteroids reduce chronic oxygen dependence to 28 days and 36 weeks of GA if administered systematically in the first 96 hours of life (they strongly improve pulmonary mechanics and gas exchange and reduce inflammatory cells and their products in tracheal aspirate) [17].

The important and well-known aspects of systemic steroids concerning increased mortality and its adverse effects on neurological outcomes (reduction of the white matter, thalamus and the basal ganglia) and on the lung structures limit their use beyond the first week of life in ventilator-dependent neonates with severe and persistent pathology. Hydrocortisone has not shown beneficial effects except in patients exposed to chorioamnionitis in the uterus [17].

Table 1. Currently used medications for selective pulmonary vasodilation.

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| <ul style="list-style-type: none"> • Endothelin antagonists • Prostacyclin analogues • Inhaled prostacyclins • Sildenafil therapy • Inhaled nitric oxide • Phosphodiesterase inhibitor pentoxifylline |
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The advantage of the use of betamethasone by inhalation has been the reduced need to use systemic steroids, while a recent analysis has demonstrated an increased incidence of success of extubation with inhaled cortisone administered for 1 to 4 weeks, but with less beneficial effects on the incidence of BPD compared to therapy with systemic steroids [19].

A promising strategy for prevention of BPD is represented by prophylactic endotracheal administration of recombinant antioxidant enzymes capable of reducing inflammatory alterations and severe pulmonary injury associated with oxygen therapy and mechanical ventilation without associated toxic effects.

Finally, clinical trials for validation of the use of progenitors of mesenchymal and angiogenic stem cells or cell biomarkers of BPD progression appear to be useful in a new diagnostic and therapeutic approach to BPD [2, 19].

Declaration of interest

The Authors declare that there is no conflict of interest.

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