Broncho-Pulmonary Dysplasia and Mechanical Ventilation

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Bronchopulmonary dysplasia is a disease particular to premature infants. It is associated with increased morbidity and mortality and its spectrum of causes and consequences has changed over the last several years. Originally described in 1967, the disease was then a disease of neonates who were less premature but more exposed to adverse ventilation and hyperoxia. Over the past 3-4 decades a variety of therapies have come into use which have changed the nature of lung injury initiated by postnatal exposure and have also enhanced survival of extremely low birthweight infants, thus the changing profile of bronchopulmonary dysplasia almost certainly reflects children now who are extremely premature who would not have survived previously but on the other hand are receiving greater levels of efficacious care and lesser levels of injurious care.

Mechanical Ventilation
It is now known that mechanical ventilation injures lungs. However, the role of such ventilator-induced lung injury in the pathogenesis of BPD is undergoing constant reevaluation. Under most circumstances, high levels of peak or plateau pressure, or larger tidal volumes, are considered to be injurious. This is borne out by multiple animal experiments and two clinical studies in adults. In addition, insufficient levels of lung recruitment appear to exacerbate the injury.

Definitions
The initial definition of bronchopulmonary dysplasia was a clinical one based on the requirement of supplemental oxygen and abnormal clinical and radiographic findings at 36 weeks post conception. Initially, pathology data consisted of prominent fibroproliferation with marked airway epithelial lesions, smooth muscle hyperplasia and a normal amount of pulmonary vasculature but with marked remodeling. Now the primary lesion is less fibroproliferative for reactive changes, but rather fewer, larger and simpler alveoli was left with an overall lower degree of lung development.

With the above heterogeneous set of pathologic criteria, it’s not surprising that definitions are difficult. The definition of supplemental oxygen in need at 36 weeks is itself not simple. Centres and individual clinicians vary greatly in how they use supplemental oxygen and it is also known that the use of supplemental oxygen is not a therapy whose effectiveness if predicted by the pathologic grading on histologic examination.

The overwhelming majority of infants with bronchopulmonary dysplasia have been born prematurely and over three-quarters weigh less than 1 kg. It seems to be very much a disease of prematurity with an instance of only 5% in those with birth weights of 1 ½ kg or more and 85% in those weighing less than 700 g.

Development of bronchopulmonary dysplasia
This was originally considered to be a condition of pulmonary oxygen toxicity. This is now known not to be the case. Supportive evidence for such a theory emerged with the
knowledge that such infants have lower levels of antioxidant protective systems such as
enzyme systems and vitamin ascorbic acid in addition to hypocapnia alkalosis as well as
use of high (relatively) tidal volumes. In addition, fluid balance appears to be important
whether measured as an aggregate of fluid balance or presence of a patent ductus
arteriosus. In addition, there is a strong connection between chorioamnionitis?, other sepsis
specific deficient polymorphisms of the surfactant proteins, the RC genes and the
development of bronchopulmonary dysplasia. Inflammatory mediators, particularly
interleukin-1 beta and interleukin-6, ?? molecules are high in those subsequently
developing bronchopulmonary dysplasia.

**Pulmonary vasculature**
Bronchopulmonary dysplasia is associated with impaired lung development. In this
context, pulmonary vasculature is noted to be relatively under-developed. It is not clear
whether pulmonary vascular impedance is worsened because of minor proliferative
changes or lower overall cross-sectional area, but what is characteristic is a marked
vasoconstrictive response to lower levels of ambient oxygen. Such findings have been
corroborated by invasive testing and the strong association with BPD as a risk factor for
pulmonary hypertension is well recognized. Finally, an often overlooked function of the
lung is clearance of ?? and metabolism within the pulmonary circulation. The BPD
lungs are highly inefficient in clearing endogenous catecholamines which may explain in
part some of the vascular anomalies present in ignition.

**Oxygenation and CO₂ clearance**
Children with BPD are usually dyspneic and this is grossly exaggerated with even slight
infections. A wide variety of features are found upon clinical examination and overall
the disorder is characterized by decreased compliance, flow limitation and increased
inspiratory and expiratory airway resistance.

For reasons that are not fully understood (perhaps in part related to inadequate
catecholamine clearance), systemic hypertension and development of systemic
pulmonary collateral vessels is prominent in severe BPD. These issues are difficult
issues upon which to prognosticate and can be responsible for significant impairment in
gas exchange and intrapulmonary shunting.

**Survival – morbidity/mortality**
Survival is very much better now than in years passed. Approximately 50% of patients
will develop a respiratory problem significant enough to require readmission to hospital.
In most cases, this propensity resolves over the first few years of life. Although there are
several series of children with return of reasonable lung function, long-term follow-up
studies to adulthood are lacking. It is difficult to predict the development of airways
disease including asthma or chronic bronchitis in older children.

**Prevention and treatment**
Talk of prevention of BPD implies that it can be prevented. This is almost certainly not
the case however its severity can be ameliorated. Antenatal steroids are highly effective,
particularly in combination with postnatal surfactant, reducing the severity of the disease
and bad outcome but they do not reduce the incidence of the disease. The same applies to
exogenous surfactant alone and it is possible that any intervention which reduces severity
of disease but not its incidence may increase survival in those subgroups at the highest
risk for mortality, thus increasing the overall burden of disease (prevalence) while
improving its outcome.

It is not clear how to appropriately ventilate children with lung disease of prematurity
except it would seem that extremely high tidal volumes and level of PEEP are bad and
low tidal volumes sufficiently high to prevent atelectasis appear to be good. The use of
particular modes of ventilation is of doubtful importance and high frequency oscillation
in conjunction with prenatal steroids, recruitment strategy are complex to interpret.

A more recent approach has been avoidance of mechanical ventilation and intubation,
using instead CPAP. Indeed, neonatal care often relies on non-invasive nasal CPAP with
low levels of ventilatory support. In addition, it is thought that fluid restriction and early
management of a patent ductus may result in lungs that are “less wet” and therefore less
susceptible to damage. The use of corticosteroids is extremely controversial because
although they reduce the likelihood of longterm dependency in oxygen, the downside
appears to be neurodevelopmental outcome and possibly mortality. There are many
reasons why this may be the case and therefore the routine use of large doses of
corticosteroids is not encouraged. There are a number of therapies on the horizon
including recombinant copper-zinc superoxide dismutase, use of antioxidant vitamins
(including Vitamin C and Vitamin E), inhaled nitric oxide and augmented nutrition.

**Impact of Mechanical Ventilation**

Mechanical ventilation is inseparable from lung injury in any ventilated patient.
However, the idea that neonates are especially vulnerable is complex. Recent laboratory
work suggests that because of the immunologic immaturity, high stretch ventilation may
be relatively less injurious to neonates compared with older subjects or adults. Indeed, it
appears that the mechanisms of lung expansion are fundamentally different in neonates
(more homogeneous, less injurious) that adults (more heterogeneous, more injurious).

**Conclusion**

In summary, bronchopulmonary dysplasia is a complex entity, the face of which has been
changing over the last 15-20 years and which promises to change even more. This talk
will outline the changing role of mechanical ventilation upon many of the newer
approaches to management and prevention of this important disease.
REFERENCES


