Introduction: The Definition of BPD

The definition of bronchopulmonary dysplasia (BPD), or the assignment of the diagnosis of chronic lung disease to premature infants, has evolved since lung disease in survivors was first described[1-5]. However, defining a disease by how it is treated, and the overlap between therapies for parenchymal lung disease and altered maturation of ventilatory control, including supplemental O_2[6], make a clear definition of BPD with or without significant parenchymal lung disease difficult, particularly without routine physiologic response testing and consistent criteria for using supplemental O_2 from center to center[3,7,8].

For these and other reasons, a definition that is based on treatment used is problematic and confounds attempts to understand and treat infants diagnosed with BPD.

A traditional approach to BPD is that it is a diagnosis that can be made at 36 to 40 weeks post-menstrual age (PMA) among infants born much earlier. The pathology of parenchymal lung disease accompanying the diagnosis of BPD has changed as therapies have evolved, and standard treatment now includes exogenous surfactant and gentler ventilation strategies. This has led to the distinction between "old BPD" or "new BPD" with implicit associated pathoanatomy of airways and airspaces[9]. Current criteria for clinical diagnosis of BPD include premature birth, provision of respiratory support at a specific PMA and, infrequently, physiologic testing[4,5,10]. An infant at 36 to 40 weeks PMA with an abnormal chest radiograph and elevated P_aCO_2 who requires mechanical

ventilation with eventual tracheostomy clearly has some measure of chronic lung disease of prematurity (CLD). Infants requiring much less support, e.g., 1 liter per minute of FiO_2 = 0.25, even if born at 24 to 28 weeks PMA, are less likely to have more than mild parenchymal lung disease, and the degree of pathoanatomy associated with the diagnosis of BPD, if any, is not clear[7].

A more recent approach is that the diagnosis of BPD is better construed as a constellation of findings that are predictive for future respiratory morbidity, particularly during the first year of life[11]. For infants at 1 year still requiring ventilatory support through a tracheostomy the diagnosis of BPD has been defined by clinical findings that foretell at 36 to 40 weeks PMA eventual respiratory morbidity. What is less clear, however, is how much parenchymal lung disease is present among infants at 36 to 40 weeks PMA who are not receiving mechanical support and are, e.g., eventually weaned off supplemental O_2 by 2 or 3 months after NICU discharge. We suspect that abnormal ventilatory control played a more frequent role in their "need" for, e.g., FiO_2 = 0.25 at 36 to 40 weeks PMA[6,12]. Among these infants, respiratory morbidity during the first year of life may differ qualitatively from those more severely affected, and feature obstructive sleep apnea or apnea complicating RSV or other viral infections[13-15].

Research done as part of the Prematurity and Respiratory Outcomes Project (PROP) was intended to sharpen the phenotypic understanding of BPD[10]. PROP was a multi-center study of 765 infants born between 24 and 28 weeks PMA. PROP was intended to clarify

the phenotype in terms of reduced lung volumes and lung compliance, increased airways resistance, and aberrant ventilatory control. It also included much emphasis on more recent, “predictive” approaches to the diagnosis of BPD. PROP described the components of the clinical history and treatment provided at 36 weeks PMA that were eventually associated with the use of respiratory medications, need for hospitalization for respiratory illnesses, etc., during the first year of life[11].

Traditional and recent approaches to defining and understanding the diagnosis of BPD have merit and overlap. To begin to discuss ventilatory control among infants with the diagnosis of BPD, it is important to recognize that BPD may be thought of as a pathoanatomic diagnosis, and/or as a set of clinical criteria that predict respiratory morbidity in the first year of life.

Among infants with the diagnosis of BPD, we recognize that prematurity can be associated with parenchymal lung disease that ranges from mild to severe. But we also will discuss that being born early, the fundamental problem, is associated with higher rates of both Sudden Unexpected Infant Death (SUID) and sleep-disordered breathing (SDB). To further clarify these interactions, we will discuss how even relatively mild CLD, when present, might increase risk for SUID and for the diagnosis of SDB. However, we contend that the all-encompassing label of BPD for any infant born early who is on some measure of support at 36 weeks PMA obscures these key interactions involving

ventilatory control maturation, and we believe that such a non-specific label ultimately hampers effort to improve outcomes for infants born prematurely.

Sudden and Unexpected Death among Premature Infants with Persistent Chronic Lung Disease and Immature Ventilatory Control

Infants born prematurely can have long central apneas, sometimes "extreme", 30 seconds or longer[16-18]. In the past, prolonged apnea, a severe example of ventilatory control instability, received much attention as a potential etiology for Sudden Infant Death Syndrome (SIDS) because infants born prematurely died more often suddenly and unexpectedly, and their deaths were often diagnosed as SIDS[19]. Among infants born before 28 weeks PMA the adjusted odds ratio (OR) for SIDS remains increased, compared to term infants, after Back-to-Sleep was recommended in the early 1990s[20]. Thus, although the number of SIDS cases dropped for both premature and term infants, the proportion of victims who had been born prematurely is actually higher, and in one study the fraction of all infants dying suddenly and unexpectedly who were born prematurely increased from 20.0% to 29.0% after Back-to-Sleep[21].

Among "other causes" of infant death, causes linked to premature birth are also increased[20]. Ascertaining when these "other causes" among premature infants are severe enough to be primarily responsible for relatively sudden deaths is problematic, however. Diagnosing a death as SIDS, and unexplained, when there are other, potentially non-lethal findings in the lungs, heart, or brain, makes for a particularly

challenging quandary. Furthermore, suggestion that autopsy findings in the lungs imposed intolerable work of breathing leading to death in an infant who had been stable on minimal support the same day should be viewed with skepticism. The possibility of a second "hit" involving dysfunctional ventilatory control, in the presence of moderate but otherwise non-lethal lung pathology, should be strongly considered.

Back-to-Sleep was associated with nearly 60% reduction in sudden and unexpected deaths among infants born at 24 to 28 weeks PMA. It is likely, however, that "the (successful) risk reduction strategies . . . in Back-to-Sleep involve primarily modification of extrinsic factors . . . such as sleeping position, bedding materials[20]. . ." Mechanistic studies of these factors[22] implicate dysfunctional motor behavior and ventilatory control responses by premature infants to "extrinsic factors" during prone sleep[22-29], rather than the imposition of intolerable resistive or elastic loads on mechanically-compromised respiratory systems.

At one extreme of the BPD/CLD phenotype, infants with severe parenchymal lung disease often do not survive to hospital discharge. For example, deaths among infants requiring a tracheostomy and mechanical ventilation usually occur among infants who are continuously monitored, and, consequently, are less often sudden and surprising.

For recovering preterm infants who were receiving supplemental O_2 by nasal cannula at 36 weeks PMA it is, in our opinion, more feasible that extrinsic factors addressed by

Back-to-Sleep had caused hypoxemia that was non-lethal *per se*, but that evoked only partially resolved unstable ventilatory patterns, including periodic breathing, with eventual long secondary apnea[13,30-32] (Figure 1).

"Extreme", long apneic events, the focus of earlier studies, appear to subside at ~43 weeks PMA[16], before the average age for sudden unexpected death in recovering preterm infants (44.2 to 47.8 weeks PMA)[20]. It may be that persisting vulnerability to ventilatory pattern instability, presenting with shorter, periodic apneas, is a better harbinger of sudden, unexpected death than the apparently resolved "extreme" events[33].

We accept that some measure of parenchymal lung disease is contributory when infants born very prematurely later died suddenly and unexpectedly. Hypoxemia has strong potential to elicit unstable ventilatory patterns[31,34]. Indeed, the contribution of moderate or lesser degrees of lung disease (Figure 1) to this dangerous sequence may be to make the infant more quickly hypoxemic with a given exposure to, e.g., prone position with bedding in front of the nose and mouth. The initiation of this potentially lethal sequence is likely prevented, by and large, when premature infants are placed to sleep supine.

In summary, antecedent long apneas do not appear to portend SUID. Rather, we propose that infants born early diagnosed with BPD, with even mild residual lung

disease, have a propensity for ventilatory pattern instability that puts them more at risk than infants born at term.

Maturation of Ventilatory Control in Newborns

We will now review how ventilatory control matures in term infants as a template for addressing the impact of altered maturation of ventilatory control on the approach to premature infants with or without BPD.

The ventilatory control system is responsible for ensuring oxygen (O_2) intake to meet cellular metabolic needs and carbon dioxide (CO_2) removal. This is achieved by interaction among peripheral chemoreceptors, central chemoreceptors, and neuronal groups in the pons and medulla. Rhythmic breathing is produced by a complex network of central pattern generators. The O_2 and CO_2 chemoreceptor system is integrated with central respiratory pattern generators, permitting response to changing conditions and maintenance of normoxia and normocapnia[35]. The functional maturation of primary respiratory rhythmogenesis is beyond the scope of this section. Our focus is on the maturation of O_2 and CO_2 chemoreceptor systems.

Maturation of ventilatory control begins early in gestation, as the ventilatory control system prepares to function at the time of birth. However, whether term or preterm,

infants are born with immature ventilatory control that may foster instability for weeks to months[36,37].

Ventilatory response to changes in CO_2 is mediated by both central and peripheral chemoreceptors; the traditional teaching of CO_2 sensing occurring solely at central chemoreceptors is no longer valid[35]. There are mixed data regarding how the central and peripheral CO_2 chemoreceptors mature, but in humans it seems that central CO_2 sensitivity is "more or less mature" at birth[37-39]. The function of peripheral CO_2 chemoreceptors in the carotid body in animals and humans also show little change in the first weeks of life. However, there is evidence that, while magnitude of response to a brief CO_2 stimulus remains constant from postnatal day 2 to week 8, the response time may shorten, indicating some maturation of timing of responses[40].

Peripheral O_2 chemoreception occurs primarily in the carotid bodies (CB). CBs are located at the left and right common carotid bifurcations, fostering rapid responses to changes in blood gas partial pressure. CB sensitivity to PaO_2 is low immediately after birth and requires a "resetting" period after transition from low intrauterine PaO_2 (23-25mmHg) to higher PaO_2 in postnatal life (80-100mmHg)[41]. The precise time course of this resetting is unclear, but term infants have been shown to have no detectable response to 100% O_2 in the first hours of life, compared with a significant decrease in minute ventilation in response to 100% O_2 beginning at 2-6 days of life[42,43]. The change in ventilation in response to brief exposure to 100% inspired O_2 - the Dejours test - is a

means of measuring the relative contribution to ventilatory drive provided by CB activity during hypoxemia. In longitudinal studies using Dejours tests in term infants, the magnitude of response increases until at least 10 weeks of life, suggesting maturational processes that continue several weeks after birth[40].

Maturation of the peripheral chemoreceptors involves changes in response to PaO_2 and $PaCO_2$. The combined response begins as an additive process and becomes multiplicative with maturation. That is, response to hypercarbia eventually is enhanced by hypoxemia, and vice versa. In the first weeks of life, infants have an additive controller that is highly sensitive to changes in PaO_2 concentration and making them more prone to apnea. At some point, the exact timing is unclear, there is a transition to a multiplicative controller that is less sensitive to changes in PaO_2 alone, and has more pronounced activation in response to changes in PaO_2 and $PaCO_2$[40,44].

A common form of ventilatory instability in infants is periodic breathing (PB). The appearance and disappearance of PB has been studied as an archetype for postnatal maturation of ventilatory control. (Figure 2) The classic teaching regarding term infants is that PB is absent at birth, relatively common at 2-4 weeks postnatal age, and rare by 3-6 months[37,45]. There is “early postnatal destabilization” followed by “late postnatal stabilization.” In term infants this period of “early postnatal destabilization” with frequent episodes of PB occurs during gradual maturation of CB function (Figure 2). Further details of the pathways to resolution of PB by 3-6 months and the “stabilization”

of the ventilatory system are less clear, but likely involve interactions among maturing chemoreceptors, increasing lung volumes, and smoother changes in ventilation in response to apnea[37].

The *ex utero* maturation of ventilatory control described above pertains to healthy term infants, who typically do not experience marked variations in PaO_2 and $PaCO_2$, and who do not require mechanical ventilation. Preterm infants, especially those born extremely prematurely, require varying amounts of supplemental O_2 and ventilatory support. The appropriate maturation of ventilatory control, at least at the level of the carotid body, is dependent on relative stability of PaO_2 and $PaCO_2$. This environment-responsive process is a sign of "developmental phenotypic plasticity"[35]. For example, the physiologic "resetting" of the CBs can be delayed or altered by exposing the CB to persistently low PaO_2 postnatally[42,46]. Furthermore, preterm infants requiring supplemental O_2 have blunting of O_2 chemoreflexes and altered CB maturation[47]. In particular, intermittent hypoxemia, sometimes alternating with hyperoxia due to treatment with O_2, has the potential to dramatically alter maturation[48,49]. Awareness of these types of "developmental phenotypic plasticity" is essential to understanding the relationship between the diagnosis of BPD and maturation of control of breathing.

Supplemental O_2 can stabilize breathing patterns and mitigate hypoxemia due to respiratory disease. Clinicians assigning the diagnosis of BPD must consider the

complexity of ventilatory control maturation, and the potential of exposure to hyperoxia and hypoxemia to further complicate processes that appear to be “plastic”.

Sleep-disordered Breathing (SDB) Among Infants Born Prematurely

Sudden death during presumed sleep is likely a manifestation of severely dysfunctional respiratory control whose putative impact on preterm infants was lessened, dramatically, by changes in sleep practices[19,20]. Since the success of Back-to-Sleep recent publications have addressed obstructive SDB without long central apneas, as obstructive SDB is more common among preterm infants than among infants born at term.

The Cleveland Children’s Sleep and Health Study[50] provided an early description of an increase in obstructive sleep-disordered breathing among children born prematurely. The methods included in-home 5 channel testing of children between the ages of 4 and 11. Children born before 28 weeks PMA had a rate of obstructive SDB of 7.3% compared to less than 2 % of those born at term. Among former preterm infants, the hazard ratio for obstructive SDB was 2.74.

The contribution of multiple factors, including the diagnosis of BPD, to rates of obstructive SDB among former premature infants was analyzed for the same cohort of 383 children from Cleveland, 7.3% of whom had SDB. Interestingly, Hibbs, et al., found no significant link between SDB and “traditional markers of severity of neonatal (lung) illness” (gestational age, diagnosis of BPD, duration of mechanical ventilation)[51].

However, unadjusted analyses showed xanthine use, presumably for problems with breathing pattern, to be one of two “potential risk factor(s) for SDB.”

There are potential anatomical explanations for obstructive SDB among infants and children, particularly during the first post-natal years. Factors may include chronic upper airway inflammation and edema that increases resistance, prolonged oral intubation that deforms the palate and occludes the nasal airway, acquired dolichocephaly and facial asymmetry that reduce airway cross-sectional area, and generalized hypotonia that involves muscles maintaining airway patency[52-54].

Adenotonsilllar hypertrophy is the most common anatomical cause of obstructive SDB among all children ages 3 to 6. The prevalence of adenotonsilllar hypertrophy among children younger than 3 years is not known, and its prevalence among infants and preschoolers born prematurely is not clear.

The impact of persistent immaturity of ventilatory control interacting with compromised upper and more-distal airways and airspaces is the subject of active research[55]. The classic studies on term infants by Fleming, et al., (Figure 2), propose a sequence of initial stable ventilatory pattern described above – early destabilization followed by late stabilization. In preterm infants, aberrancy in this sequence, or a delay in maturation of ventilatory control have the potential to contribute in important ways to higher rates of SDB, including obstructive SDB. The ventilatory pattern during “destabilization”

described by Fleming, et al., is periodic breathing interspersed with periodic apnea with or without intermittent hypoxemia. The relevance of this template, with aberrance or delays, is suggested by studies of caffeine's effects between 35 and 39 weeks PMA in preterm infants (born <32 weeks PMA)[56,57] (Figure 3), and among late preterm infants born between 34 and 37 weeks PMA[58]. These studies indirectly implicate periodic breathing (PB) as a cause for intermittent hypoxemia at a PMA beyond when caffeine, which treats PB very effectively, is often discontinued by NICU policy at many centers[59].

More than 25 years after its publication, Edwards, et al., analyzed Fleming's data set via calculation of loop gain[37,45] (Figure2). Loop gain analyses have been used extensively in sleep medicine to model sleep-disordered breathing in terms of the contribution of ventilatory control and the subject's ability to maintain gas exchange homeostasis. Loop gain describes the quantity of response of a system to a perturbation[60] (figure 4). For respiration, the combination of a very active "controller" and smaller lung volumes (V_L , Figure 4) effectively exchanging O_2 and CO_2 produces a system with large loop gain and more potential for oscillation and instability.

During the time period when infants had more frequent PB – 40 to 100 post-natal days of life[45] - analyses (Figure 2) showed larger loop gain, > 0.4 to 0.9[37]. A more recent study of 20 premature infants at 36 weeks PMA, who had been born between 24 and 28 weeks PMA, showed the potential association for preterm infants between larger loop gain and more frequent PB[61] (Figure 5). Another, larger study from the same cohort of

infants, at the same PMA (36 weeks), showed that > 40% of infants receiving prescribed supplemental O_2 developed oscillations in ventilatory pattern characteristic of PB when the FiO_2 was reduced[6].

The potential relevance of larger loop gain and re-emergence of PB to eventual development of obstructive SDB is suggested by studies of loop gain in older subjects, showing that severe obstructive SDB often manifests "obstructive cycling" that is periodic[62,63] (Figures 6 a and 6b). Furthermore, the likelihood that recovering premature infants' $PaCO_2$ may be just above their apneic threshold, as is sometimes the case for adults with obstructive cycling, may help explain these infants' propensity for obstructive SDB.

Using analysis of loop gain as their method, Domany et al. studied the ventilatory control "phenotype" of 63 former preterm infants referred for polysomnography at 0.5 to 7 years of age[15]. The 26 with obstructive SD had event indices > 2/hr. They used cluster analysis to identify which of the 2 components of loop gain (Figure 4) – controller gain or plant gain (the blood gas response to a change in ventilation) – better characterized infants with more obstructive SDB. The clusters with progressively more obstructive SDB had larger plant gain, with no overall change in loop gain *per se*.

Taken together, these findings suggest that if infants born prematurely do not develop and maintain the post-natal stabilization described for term infants[45] (Figure 2), preterm

infants may be at particular risk for developing obstructive SDB. This is perhaps in part because of abnormalities in maturation of ventilatory control that persist during childhood and recovery from CLD. “Exposures” causing hypoxemia, which can elicit PB in susceptible subjects, e.g., RSV infection[13], or development of adenotonsilllar hypertrophy may elicit “destabilization” among former preterm infants, who have not completely resolved their propensity for respiratory pattern instability[64] (Figure 6).

Clinicians caring for preterm infants after NICU discharge, with or without the diagnosis of BPD, should be aware of their increased risk for obstructive SDB[50,52]. If the infant gasps for breath during sleep, snores, sleeps restlessly with stertorous breathing, has poor growth, etc., overnight polysomnography with oximetry should be obtained. Clinicians should be aware that whatever anatomic factors might be in play, there may also be an important contribution of delayed maturation of ventilatory control. Furthermore, infants diagnosed with BPD often may have only mild parenchymal lung disease (CLD). But the residual lung disease may be sufficient to cause desaturations of > 3% with even short reductions in airflow, causing the brief reduction in SpO_2% to be scored as a respiratory event during polysomnography. Thus, interactions between parenchymal lung disease and ventilatory instability have practical, clinical implications.

Implications of the Overlap of the Diagnosis of Bronchopulmonary Dysplasia and Immature Ventilatory Control

The persistence of immature and dysfunctional ventilatory control beyond 36 to 40 weeks PMA, and even well beyond the NICU course, is likely underappreciated[7]. We propose that the apparent increase in rates of sleep-disordered breathing, and obstructive SDB, among former preterm infants who are preschoolers and older can plausibly be explained by unmasking persistent aberrant ventilatory control that arose during the NICU stay.

The use of caffeine, a widespread practice in NICUs, has been associated with fewer infants being diagnosed with BPD. It seems likely, however, that the beneficial effects of caffeine are due to its direct effect on stabilizing ventilatory pattern and SpO_2%[56,57], rather than a direct amelioration of CLD, as some have suggested. Studies allowing prolongation of caffeine treatment by clinical decision have shown less intermittent hypoxemia, suggesting that discontinuation of caffeine in many centers following NICU protocols at, e.g., 34 weeks PMA, could be reconsidered. Clinicians should be aware of risk for resumption of PB when deciding to discontinue caffeine for apparently stable infants still prone to destabilization even at 36 to 40 weeks, particularly if the infant experiences transient spontaneous hypoxemia[56] (Figure 3). Hypoxemia can trigger PB[31,34] and PB can foster continued and worsening intermittent hypoxemia[65] (Figure 1). Finally, caffeine use in neonates appears to have the potential to permanently enhance maturation of ventilatory control, a type of therapy-induced “neuroplasticity” whose effects may persist into adulthood[66].

The lack of clear phenotypic specificity is a potential source of confusion in studies of causes and therapies for BPD. This obfuscation is perhaps the most important effect of under appreciation of immature and dysfunctional respiratory control at 36 to 40 weeks PMA. ("If the neonatal community does not have good names for the respiratory syndromes we see, then data bases will be most problematic[7]."")

For one large, multi-center study (PROP) it appears that delayed ventilatory control maturation might have underlain some clinicians' decisions to treat with supplemental O_2 for many infants.

In PROP the originally agreed-upon, disease-defining criterion for the diagnosis of BPD was a physiologic challenge test for infants receiving support via nasal cannula (infants at 36 weeks PMA intubated or receiving trans-nasal mechanical support were assigned the diagnosis of BPD without challenge tests, 55 infants, 26% of those diagnosed with BPD). Infants receiving supplemental O_2 alone were to have a stepwise reduction in FiO_2 and flow rate delivered. Failure to maintain SpO_2% > 90% during the challenge was to have meant that the infant was assigned the diagnosis of BPD. Challenge tests were completed in 642 of 765 infants (83.9%) eventually included in the PROP cohort[5]. However, in the course of PROP the decision was made at some centers to forego room air challenges and their results, and to assign the diagnosis of BPD using a traditional criterion[2] of receiving supplemental O_2. In the end, this traditional criterion was used in the analysis of PROP infants and data, rather than the physiologic challenge.

It is apparent that there are substantial problems with the treatment-based approach eventually used to assign the diagnosis of BPD in PROP, and in NICUs in general, while foregoing physiologic challenges. As summarized by one author, "Strategies for primary prevention [of BPD] are stymied by methodologic obstacles, not the least of which is… defining a disease by its treatment, and the use of a definition that provides no information about pathophysiology, disease progression, or phenotypic variability…[3]" In PROP 30.1% of 266 infants challenged passed the reduction to room air test but were still classified as BPD because they were receiving supplemental O_2. And at a single center, where respiratory patterns were recorded during the room air challenge, a large majority (63.8%) of those who failed did so with diminished respiratory effort or periodic breathing[6]. In summary a plausible estimate is that nearly ¾ of infants (74.4%) assigned the diagnosis of BPD in a very large, multi-center study, either did not meet the original disease-defining criterion, or, even with residual parenchymal lung disease, had significant contribution of immature and dysfunctional ventilatory control driving their need for supplemental O_2.

Among infants diagnosed with BPD, future clinical studies of causes and treatment in large cohorts of preterm infants will be strengthened if investigators have some measure of how often, at 36 weeks PMA and beyond, the need for supplemental O_2, and, perhaps, high-humidity, high-flow nasal cannula with relatively low FiO_2, is being more or less driven by immature and dysfunctional ventilatory control. To expedite

clinician's access to some insight into ventilatory control, studies are underway to validate physiologic biomarkers for maturation of ventilatory control by measurements that are relatively easy to acquire[61] (Figure 5).

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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