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EDITORIAL

Sildenafil therapy for bronchopulmonary dysplasia: not quite yet

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Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy and complicates the course of up to one-third of extremely preterm babies. BPD results in poor long-term pulmonary outcomes and increases the risk of neurodevelopmental delay. As a result, a significant amount of research has sought to better define the population most at risk, as well as to develop prevention strategies.[1,2] We now understand that the risk for BPD increases with younger gestational age, intrauterine growth restriction, presence of chorioamnionitis and delay in time to full enteral feeds.[2,3] However, the ability to identify populations of at risk infants has not improved our ability to prevent BPD. Although prenatal steroids and postnatal surfactant have diminished the impact of respiratory distress syndrome, they have not diminished the frequency or severity of BPD in the extremely low birthweight population.[2,4] In recent years, various strategies such as hydrocortisone, recombinant human superoxide dismutase, vitamin A, caffeine and, most recently, inhaled nitric oxide have all been tested as BPD-prevention strategies, but with a variable degree of success.[5–12] To date, there is no absolute therapy to prevent BPD other than to prevent preterm birth.

As smaller and younger babies survive with BPD, the complication of BPD-associated pulmonary hypertension (PH) has gained recognition. BPD-associated PH occurs in 30 to 45% of infants with moderate to severe BPD (as defined by the NIH consensus criteria).[13–16] The exact etiology of this PH is poorly understood, although recent evidence from both animal and human studies suggests that intrauterine growth restriction increases risk for BPD-associated PH.[14,17,18] Early injury to the developing lung impairs both alveolarization and angiogenesis, and emerging evidence indicates that preterm birth at an early stage of lung development produces a developmental arrest of pulmonary vessel formation.[19] Other factors, such as exposure to supraphysiological oxygen levels, lead to remodeling and pruning of the remaining small pulmonary vessels, producing vascular dysfunction and PH. Over time, this PH contributes to ongoing hypoxemia, which induces further vascular remodeling and eventually leads to right ventricular hypertrophy.[20] In the most severe cases, right ventricular hypertrophy progresses to right ventricular failure, cor pulmonale and death.[21] Although we still need to learn more about the epidemiology and outcomes, several case series suggest that the mortality in infants with BPD-associated PH approaches 50% by 2 years of life, and there is tremendous concern about the ability of surviving infants to reach adulthood and whether this neonatal illness will create lasting residual deficits.[15,22]

Although there continues to be a major focus on prevention, we also need safe and effective therapies to treat infants who have already developed BPD and BPD-associated PH. Over the years, many therapies including diuretics, inhaled bronchodilators and steroids have been attempted to improve the pulmonary function in infants with significant BPD. However, no clearly effective therapy has emerged that improves pulmonary mechanics without important side effects.[4,23] Even less is known about appropriate therapy for BPD-associated PH.

There is considerable evidence that nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) signaling is disrupted by preterm birth, lung injury and neonatal PH, which has generated interest in therapies targeted toward this pathway.[24,25] For instance, inhaled nitric oxide acutely improved PA pressures during cardiac catheterization of infants with BPD-associated PH, but its long-term efficacy remains uncertain, and logistical challenges limit its use in the outpatient setting.[26] Sildenafil is a selective cGMP-specific phosphodiesterase inhibitor that was recently approved for the treatment of adult pulmonary arterial hypertension.[27] Interestingly, PH and therapies such as oxygen may increase expression and activity of cGMP-specific phosphodiesterases, which would be expected to lower cGMP concentrations and exaggerate PH.[28] Sildenafil was recently investigated in term infants as a potential therapy for persistent PH of the newborn (PPHN). Oral sildenafil improved survival in small cohort of term infants with PPHN vs placebo (85% vs 17%),[29] and a recent pilot trial of intravenous sildenafil showed acute improvements in oxygenation in infants treated with or without iNO.[30] As oxygenation index was used as the endpoint, it was unclear whether the improvement seen with sildenafil was purely due to its vascular effects or whether there might have been some improvement in lung function as well.

The availability of sildenafil as an enteral preparation makes it feasible for long-term therapy for infants with BPD. In rodent models of BPD, sildenafil improved alveolarization and decreased BPD-associated remodeling of the pulmonary vasculature and right ventricular hypertrophy.[31,32] More recently, Mourani *et al.*[22] described that long-term treatment with chronic oral sildenafil was well tolerated in infants with chronic lung disease and PH, and improved echocardiographic findings of PH, including decreased systolic pulmonary artery pressure and reduced septal flattening.

In this issue of *Journal of Perinatology*, Nyp *et al*. extends these studies by providing an additional large case series of 21 infants that explores whether oral sildenafil produces short-term improvements in pulmonary hemodynamics and gas exchange in infants with moderate to severe BPD-associated PH. As noted in other case series, the authors found a high number of SGA infants in their population.[14] Patients were >5 months old at the time of sildenafil initiation, and at a median of 49 weeks corrected gestational age. Sildenafil was well tolerated, with transient hypotension observed in only one infant. Although sildenafil acutely decreased PA pressures, unlike PPHN, there was no improvement in pulmonary gas exchange. Concurrent use of iNO did not appear to affect the response to sildenafil.

Nyp's findings highlight the challenging, multifactorial nature of the clinical problem. PPHN in term infants is most commonly a delayed vascular transition from intrauterine to extrauterine life. Even infants with vascular remodeling or hypoplasia often experience short-term improvements in oxygenation. In contrast, the infant with BPD-associated PH has both vascular hypoplasia and vascular remodeling in conjunction with alveolar simplification and parenchymal lung disease. Although Nyp's study provides additional evidence that sildenafil improves the hemodynamic findings of PH, a fixed component of vascular or parenchymal dysfunction appears to remain. Furthermore, long-term outcome data are still needed to determine whether benefits are sustained and whether reductions in PA pressure will improve long-term outcomes. We agree with the authors that chronic sildenafil therapy for BPD-associated PH should be approached cautiously at present, and hope that despite the considerable challenges, appropriate clinical studies will answer these important questions.

Conflict of interest

The authors declare no conflict of interest.

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References

1 Walsh MC, Szefler S, Davis J, Allen M, Van Marter L, Abman S *et al.* Summary proceedings from the bronchopulmonary dysplasia group. *Pediatrics* 2006; **117**(3 Part 2): S52–S56.
2 Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; **163**(7): 1723–1729.
3 Wemhoner A, Ortner D, Tschirch E, Strasak A, Rudiger M. Nutrition of preterm infants in relation to bronchopulmonary dysplasia. *BMC Pulm Med* 2011; **11**: 7.
4 Thomas W, Speer CP. Nonventilatory strategies for prevention and treatment of bronchopulmonary dysplasia—what is the evidence? *Neonatology* 2008; **94**(3): 150–159.
5 Ambalavanan N, Wu TJ, Tyson JE, Kennedy KA, Roane C, Carlo WA. A comparison of three vitamin A dosing regimens in extremely-low-birth-weight infants. *J Pediatr* 2003; **142**(6): 656–661.
6 Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD *et al.* Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med* 2006; **355**(4): 343–353.
7 Kinsella JP, Cutter GR, Walsh WF, Gerstmann DR, Bose CL, Hart C *et al.* Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med* 2006; **355**(4): 354–364.
8 Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; **354**(20): 2112–2121.
9 Tyson JE, Wright LL, Oh W, Kennedy KA, Mele L, Ehrenkranz RA *et al.* Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med* 1999; **340**(25): 1962–1968.
10 Watterberg KL, Gerdes JS, Gifford KL, Lin HM. Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. *Pediatrics* 1999; **104**: 1258–1263.
11 Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC *et al.* Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. *Pediatrics* 2004; **114**: 1649–1657.
12 Davis JM, Parad RB, Michele T, Allred E, Price A, Rosenfeld W. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* 2003; **111**(3): 469–476.
13 An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK *et al.* Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. *Korean Circ J* 2010; **40**(3): 131–136.
14 Check J, Harvey C, Matoba N, Porta N, Gotteiner N, Mestan K (eds). *Intrauterine Growth Restriction in BPD Infants with Pulmonary Hypertension: A Case-Control Study*. Pediatric Academic Societies: Denver, 2011.
15 Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC *et al.* Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007; **120**(6): 1260–1269.
16 Kim DH, Kim HS, Choi CW, Kim EK, Kim BI, Choi JH. Risk factors for pulmonary artery hypertension in preterm infants with moderate or severe bronchopulmonary dysplasia. *Neonatology* 2011; **101**(1): 40–46.
17 Rosenberg A. The IUGR newborn. *Semin Perinatol* 2008; **32**(3): 219–224.
18 Rozance PJ, Seedorf GJ, Brown A, Roe GB, O'Meara MC, Gien J *et al.* Intrauterine growth restriction decreases pulmonary alveolar and vessel growth and causes pulmonary artery endothelial cell dysfunction *in vitro* in fetal sheep. *Am J Physiol Lung Cell Mol Physiol* 2011 (doi:10.1152/ajplung.00197.2011, e-pub ahead of print).
19 Thebaud B, Abman SH. Bronchopulmonary dysplasia: Where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. *Am J Respir Crit Care Med.* (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review). 2007; **175**(10): 978–985.
20 Aslam M, Baveja R, Liang OD, Fernandez-Gonzalez A, Lee C, Mitsialis SA *et al.* Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease. *Am J Respir Crit Care Med* 2009; **180**(11): 1122–1130.
21 Hislop AA, Haworth SG. Pulmonary vascular damage and the development of cor pulmonale following hyaline membrane disease. *Pediatr Pulmonol* 1990; **9**(3): 152–161.
22 Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009; **154**(3): 379–384, 384.e1–2.
23 Pantalitschka T, Poets CF. Inhaled drugs for the prevention and treatment of bronchopulmonary dysplasia. *Pediatr Pulmonol* 2006; **41**(8): 703–708.

24 Afshar S, Gibson LL, Yuhanna IS, Sherman TS, Kerecman JD, Grubb PH *et al.* Pulmonary NO synthase expression is attenuated in a fetal baboon model of chronic lung disease. *Am J Physiol Lung Cell Mol Physiol* 2003; **284**(5): L749–L758.

25 Bland RD, Ling CY, Albertine KH, Carlton DP, MacRitchie AJ, Day RW *et al.* Pulmonary vascular dysfunction in preterm lambs with chronic lung disease. *Am J Physiol Lung Cell Mol Physiol* 2003; **285**(1): L76–L85.

26 Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2004; **170**: 1006–1013.

27 Rubin LJ, Badesch DB, Fleming TR, Galie N, Simonneau G, Ghofrani HA *et al.* Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: SUPER-2. *Chest* 2011 (doi:10.1378/chest.10-0969, e-pub ahead of print).

28 Farrow KN, Groh BS, Schumacker PT, Lakshminrusimha S, Czech L, Gugino SF *et al.* Hyperoxia increases phosphodiesterase 5 expression and activity in ovine fetal pulmonary artery smooth muscle cells. *Circ Res* 2008; **102**(2): 226–233.

29 Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. *Pediatrics* 2006; **117**(4): 1077–1083.

30 Steinhorn R, Kinsella J, Pierce C, Butrous G, Dilleen M, Oakes M *et al.* Intravenous Sildenafil in the Treatment of Neonates with Persistent Pulmonary Hypertension of the Newborn. *J Pediatr* 2009; **155**(6): 841–847.

31 de Visser YP, Walther FJ, Laghmani el H, Boersma H, van der Laarse A, Wagenaar GT. Sildenafil attenuates pulmonary inflammation and fibrin deposition, mortality and right ventricular hypertrophy in neonatal hyperoxic lung injury. *Respir Res* 2009; **10**: 30.

32 Ladha F, Bonnet S, Eaton F, Hashimoto K, Korbutt G, Thebaud B. Sildenafil improves alveolar growth and pulmonary hypertension in hyperoxia-induced lung injury. *Am J Respir Crit Care Med* 2005; **172**: 750–756.