Pulmonary Arterial Hypertension in Infants with Chronic Lung Disease: Will We Ever Understand It?

Thomas J. Kulik, MD, Lawrence M. Rhein, MD, and Mary P. Mullen, MD, PhD

We are at an awkward stage in our understanding of how the pulmonary circulation impacts the clinical phenotype of infants with chronic lung disease (CLD) and what optimal management of the "lesser" circulation in these babies might be. We know that pulmonary arterial hypertension (PAH) can cause morbidity, but it is unclear how high pulmonary arterial pressure (PAP) must be to be relevant. The literature implies that even moderately increased PAP can be harmful,[1-3] but with cardiac malformations causing right ventricular (RV) hypertension from birth, RV systolic pressure (RVP) at systemic levels is well tolerated,[4] suggesting that clinical findings attributed to PAH may sometimes actually originate elsewhere. And even when PAH is harmful, the temptation to use vasodilator drugs helpful in other contexts should be balanced by the lack of data regarding their usefulness with CLD. In short, although we know that PAH can be a liability, we don't know who will benefit from treatment or which, if any, of the available drugs will be salutary. Despite these lacunae, caregivers are sensitized to the pernicious effects of PAH, with potentially unfavorable consequences: We have observed that PAH can be the caregiver's major concern, even in infants whose most serious liability is actually abnormal gas exchange. Preoccupation with PAH can negatively impact care because it can detract from focusing on issues of larger consequence (eg, optimizing ventilatory management and nutrition)[5]; and anecdotal and published evidence indicates increasing use of enteral and parenteral vasodilator drugs in these patients. These agents lack approval from the Food and Drug Administration for this indication, the most recent expert consensus view notes that they are of unproven benefit and not recommended with CLD,[6] and for every theoretical reason they might be helpful, there is also one to suggest possible harm. Moreover, the widespread use of long-term vasodilators may complicate efforts to develop rational therapy.

We suggest that until we know *which* infants with CLD should be treated for PAH and that the "therapy" used actually *makes the patient better*, the unstructured use of vasodilators in infants with CLD should be discouraged. Two notions underlie these arguments: (1) Although severely increased PAP is bad, how often moderate PAH (defined here as RVP < systemic) has significant clinical impact is unknown; (2) It is possible that available vasodilators are helpful, but CLD-associated PAH is sufficiently different from the forms of PAH where such medications are clearly useful that extrapolation from one to the other is problematic.

BPD	Bronchopulmonary dysplasia
CI	Cardiac index
CLD	Chronic lung disease
PA	Pulmonary artery
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
RAP	Right atrial pressure
RVP	Right ventricular pressure
RV	Right ventricular

PAH is Associated with CLD

Abman[1] and others[3,7] have cogently made the case for the importance of PAH in CLD, but data are lacking regarding the quantitative relationship between PAP and disability. Khemani et al[3] reported an unselected series of 42 infants with bronchopulmonary dysplasia (BPD); 16 died, with PAH believed to be a "proximate contributing factor, often in concert with respiratory failure" in 14, a determination made because of a history of hemodynamic instability out of proportion to O_2 requirement and ventilatory settings. However, the fact that respiratory failure—which is seldom associated with demise with other types of PAH—was present suggests that pulmonary dysfunction was a significant contributor. They found that PAP ≥ systemic was associated with shorter survival, but not severe lung disease, although the effect of subsystemic PAH on the clinical phenotype was not reported.

What Is the Relationship Between PAP and Clinical Disability?

Cardiac malformations with systemic RVP from birth or later in infancy (eg, valvar pulmonic stenosis) generally have few or no symptoms related to the RV hypertension. For example, in a report of infants and children with valvar pulmonic stenosis,[8] the cardiac index (CI) was generally normal; the right atrial pressure (RAP) was also normal (<5 mm Hg) in 16 of 26 studies in patients < 3 years old, and only mildly

From the Pulmonary Hypertension Program, Department of Cardiology, Division of Cardiac Critical Care (T.K., M.M.) and the Divisions of Newborn Medicine and Pulmonology, the Department of Medicine, (L.R.), Children's Hospital Boston, and Harvard Medical School, Boston, MA

The authors declare no conflicts of interest.

 10.1016/j.jpeds.2010.03.022

elevated in the rest (<8 mm Hg). All patients were symptom free save for 2 with severe RV hypertension.

Pulmonic stenosis is not strictly analogous to PAH, because RV afterload in early and late ventricular ejection is higher in patients with PAH than those with valvar narrowing. More pertinent to PAH are patients with Eisenmenger, who have high PA diastolic pressure (often with the additional liability of cyanosis) yet RV function is good for many years.[4,9] Other malformations with systemic RVP, such as tetralogy of Fallot, have no obvious RV phenotype in the young. Indeed, the general rule is that the right ventricle adapts well to increased RVP present since birth, its function is preserved for years, and heart failure is absent.[4] Assuming that infants with PAH caused by CLD have increased PAP in the neonatal period, one might expect their RV to be similarly well adapted to increased afterload.

Possibly neonates with CLD have a "honeymoon" period, where PAP falls (and the RV becomes "deconditioned") before later development of PAH. Even if so, it seems likely that the infant RV would rapidly adapt to increased pressure: when babies in the first year of life with d-transposition of the great arteries and low left ventricular pressure have an acute increase in *left* ventricular afterload imposed with a PA band, the ventricle rapidly acquires mass and becomes capable of generating systemic pressure within days.[10] No analogous information exists for the human RV, but lambs quickly have development of RV hypertrophy and increase systolic function with chronic PA banding, albeit with reduced compliance.[11]

Hemodynamics in Infants with CLD

Even if moderate RV hypertension little affects infants with cardiac defects, PAH may have greater clinical impact with CLD; are there hemodynamic data available for these patients? We know of 17 articles describing catheter studies, mostly of infants with BPD, which include, at a minimum, PAP.[2,3,7,12-24] Indication for catheterization was inconsistently defined, but many subjects with significant symptoms were studied. Six of these reports include CI, as well as PAP.[2,3,13,15,17,19] CI was normal in most patients with CLD, even those with RVP > systemic, and there is no level of PAP that discriminates low from normal CI.

Information relating to RV filling pressures is limited, although they are usually at most mildly increased. Harrod[18] reported that RV end-diastolic pressure in 6 patients with BPD ranged from 5 to 9 mm Hg (4 were < 6 mm Hg, with normal being < 5 mm Hg), with PA systolic pressures ranging from 32 to 65 mm Hg. Mourani et al[22] reported an average mean RAP of 6.2 mm Hg in 10 patients with BPD with an average mean PAP of 34.1 mmHg. A subsequent article from the same group reported a mean RAP of 8 ± 2 mm Hg in 31 young children with CLD, with an average mean PAP of 35 ± 12 mm Hg.[7]

Echocardiographic data regarding RV size and systolic function is very limited. Berman et al measured RV dp/dt in 9 patients with BPD (average RVP = 60 mm Hg, range 30 to 105 mm Hg) and found dp/dt was increased relative to normal but similar to that observed in other types of patients with RV hypertension but normal function.[13] Although dp/dt is an imperfect measure of RV function, this is perhaps the best available data regarding RV performance in infants with PAH related to CLD.

Another way of assessing the impact of afterload on RV function is to measure the effect of *acute afterload reduction* on RV output. There are 6 reports of vasodilator trials in patients with BPD.[2,3,15,16,19,22] In 4 trials a nonselective vasodilator was used (hydralazine, calcium channel blockers, prostacyclin), and inhaled nitric oxide was used in 3. For studies of nonselective vasodilators, the average baseline mean PAP ranged from 34 to 69 mm Hg; for iNO, baseline mean PAP was 34 to 52 mm Hg. In 3 of the nonselective vasodilator trials, RV output (CI) increased acutely, but in 2 of these PAP fell little, suggesting that the increased output was not due to relief of RV afterload but rather to other factor(s) (for example, systemic vasodilation). The nitric oxide trials also suggest that RV output was not limited by RV afterload because a fall in PAP was accompanied by increased CI in only 1 of the 3 trials.

To summarize, there is no consistent relationship between PAP and CI in infants with CLD; some have reduced CI, and many have normal CI despite considerable PAH. Vasodilator studies in patients with CLD and PAH suggest that RV output is often *not* limited by RV afterload. In short, available data indicate that PAH can compromise the circulation in some patients with CLD, but that others adapt well to RV hypertension, at least by classical hemodynamic parameters.

However, hemodynamic measurements only partially describe the clinical state of a patient with heart or lung disease, and other considerations are important: (1) Catheterization laboratory hemodynamics may poorly reflect those encountered in life, especially when the patient is stressed with respiratory infection or other insults; (2) congestive heart failure is not always reflected in resting hemodynamics. Neurohumoral system activation impacts the clinical phenotype[4] but is incompletely revealed by hemodynamic variables; and (3) consequences of PAH other than RV dysfunction (eg, increased lung stiffness) may be significant yet not manifest in the data reviewed. One is forced to conclude that, despite multiple hemodynamic studies, the quantitative relationship between PAP and clinical disability remains murky.

Pulmonary Vasodilators with CLD: Safe/Effective/Both/Neither?

There are multiple ways vasodilators could, theoretically, be helpful in patients with CLD: decreasing PAP by reducing resting vascular tone or reactivity, or by increasing the cross-sectional area of resistance vessels via reducing pathologic remodeling or promoting healthy remodeling of the circulation. They may also have favorable nonvascular effects: for example, sildenafil increases alveolar and capillary