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Bronchopulmonary Dysplasia and Pulmonary Hypertension in Need of Cardiologist Innovation and Research

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Abstract

A major cause of mortality in premature infants with bronchopulmonary dysplasia (BPD) is the formation of pulmonary hypertension (PH). Early, accurate screening and diagnosis is essential for the prevention and treatment for this complication. Routine screening for PH among BPD patients may be considered in light of higher odds of morbidity and possible short and long-term morbidities. The questions that remain unanswered are; when and how to improve the accuracy of echocardiography. Cardiac catheterization remains the gold standard for diagnosis and prognostication of pulmonary hypertension. However, due to risks with catheterization, echocardiography has become the mainstay for screening, diagnosis and follow-up during treatment. In determining the modality of screening and diagnosis, it is important to understand the limitations and risks associated with each method. More cardiologists are needed that are interested in these questions and are ready to innovate and possibly create a registry for this population.

Keywords: Bronchopulmonary dysplasia; Pulmonary hypertension; ECHO; Cardiac catheterization

Introduction

The incidence of bronchopulmonary dysplasia (BPD) in the literature ranges from 4.6% to 72% [1,2]. This broad range may be explained by the heterogeneity of the studied populations. Retrospective studies report that pulmonary hypertension (PH) may occur in up to 17 to 43% of preterm infants with BPD [3-6]. Pulmonary hypertension was diagnosed by echocardiogram in 23% of infants with severe BPD [7-10]. In a retrospective study, of all infants<32 weeks GA born between 2004 and 2008, PH occurred initially at a median age of 65 days (range: 7-232 days) [4]. Retrospective studies of infants with BPD-associated PH have reported mortality rates ranging from 14 to 38% [4,6]. In a more recent study, 38% of these infants die within 6 months of diagnosis and only 25% survived to 2–3 years age [3].

Despite this data demonstrating the importance of bronchopulmonary dysplasia-associated pulmonary hypertension and its increased morbidity and mortality, there is paucity of clinical and prospective trials addressing interventions to improve diagnosis and early screening of this co-morbidity.

This review aims to comprehensively discuss and highlight screening and diagnostic approaches in patients with PH and BPD and proposes further research in this area.

Discussion

Bronchopulmonary dysplasia (BPD) has become one of the most common pathologies in premature infants [6,11-13]. A major complicating factor and key cause of mortality in this population is PH [3,14-17].

The 'new' BPD is characterized by decreased numbers and volume of alveoli and size of intra-acinar pulmonary arteries resulting in a significant reduction in the total cross-sectional area of the pulmonary vascular bed [16-18]. This reduction, in conjunction with alveolar hypoxia that results in structural remodeling of the pulmonary vasculature, gives rise to abnormal vasoreactivity and subsequently contributes to the development of PH [18-21]. Pulmonary hypertension is characterized by vasoconstriction and abnormal remodeling of pulmonary vessels, leading to a progressive increase in pulmonary artery pressure (PAP), and vascular stiffness. This increase in PAP, over the long term, leads to an increase in right ventricular (RV) afterload resulting in RV hypertrophy and failure [22-26].

Although the mechanisms responsible for elevated pulmonary vascular resistance and altered reactivity are not completely understood, the development of PH is a recognized and sometimes serious complication of BPD that can

contribute significantly to the morbidity and mortality rates of preterm infants [3,19,27]. Furthermore, premature infants with BPD and severe PH are at high risk of death, particularly within the first six months after diagnosis of PH [28].

One prospective trial attempted early diagnosis of PH by echocardiogram (ECHO) between 4 to 6 weeks of life in all extreme low birth weight (ELBW) born between 2008 and 2011. They were only able to identify one-third of infants diagnosed with PH following this protocol [12]. The diagnosis of PH in infants and neonates in the context of BPD is challenging and requires a high degree of suspicion because the signs and symptoms may be subtle, non-specific and masked by underlying BPD, even in infants with significantly elevated pulmonary artery pressure. Doppler echocardiography (DE) is a non-invasive test commonly used to screen and manage PH but has limitations as a screening strategy.

Previous studies in adults and children assessed the validity of ECHO measurements performed simultaneously with cardiac catheterization measurements show good correlation [29-31]. The most common quantitative method for determination of PH is tricuspid regurgitation (TR) jet velocity utilizing the modified Bernoulli equation to determine the right ventricular systolic pressure (RVSP=4v2 added to the right atrial pressure, where v=TR jet velocity) [26]. This has its limitation. Specifically, echocardiography could fail to detect a measurable (TR) jet velocity in a significant number of high-risk patients and that the absence of a TR jet velocity does not rule out the presence of severe PH [6,12,32,33]. In available studies done in neonates with chronic lung disease, systolic PAP could be estimated in 61% of ECHO studies, but there was poor correlation with catheterization [32]. Specifically, in infants with BPD, more than moderate TR on echocardiography was observed in only 28% of the infants with PH. Other measures of PH, such as right atrial enlargement and septal flattening, seem to have good sensitivity and a positive predictive value for diagnosing PH in children with BPD; however, the specificity and negative predictive value are poor [4].

Further studies involving the utilization of non-invasive transthoracic echocardiography in determining pulmonary arterial systolic pressure (PASP) as a surrogate of right heart catheterization (RHC) estimates are based on single center results. These studies have been called into question by more recent studies with indications that misclassification of clinical PASP it greater than 54% of cases [34]. In patients with pulmonary hypertension, there was only moderate correlation between DE and RHC in determining PASP (r=0.68, p=0.001) with overestimation in 40.7% and underestimation in 59.3% of cases. Doppler echocardiography was inaccurate in 50.6% of cases [35].

Once right ventricular hypertension is present, the accuracy of DE is diminished in determining right ventricular systolic pressure (RVSP) as compared to catheterization.

As RVSP increases ≥ 1/2 SBP and ≥ 2/3 SBP, PPV is 86% and 81% while NPV is 86% and 88% respectively. Thus, echocardiography was inaccurate in 24% of patients with RVSP ≥ 1/2 SBP and in 33% of patients with RVSP ≥ 2/3 SBP. This has been demonstrated in both adult and pediatric studies [35-38]. A retrospective study in 2017 demonstrated by utilizing an RSVP ≥ 35 in conjunction with multiple other echocardiographic variables (enlarged right atria, abnormal right ventricle, dilated pulmonary artery, etc.) increased sensitivity and specificity [39]. This was an adult study and requires enough time for other cardiac changes to develop. Thus, despite advances in technology, DE alone is not a reliable tool.

Cardiac catheterization is the definitive confirmatory test for PH (mean pulmonary artery pressure (mPAp)>25 mmHg, PVR>3 Wood units × m^2, or pulmonary capillary wedge pressure ≤ 15 mm Hg) [40]. This further allows prognostication of PH by defining ratio of mPAp to mean systemic artery pressure, PVR to systemic vascular resistance, elevated right atrial pressure, and indexed PVR>20 Wood unit's × m^2, and the persistence of positive vasoreactivity testing [41]. Catheterization now is reserved or considered when severity is unknown, when the patient is not responsive to therapy as expected, for evaluation of secondary causes, or to determine responsiveness to therapies [42-45]. It is important to note that morbidity and mortality from catheterization ranges from 1% to 6% of cases. This increases in small and ill patients [26,40].

We suggest, based on the algorithm proposed by the BPD Collaborative for infants at risk for PH, early echocardiograms for the diagnosis of PH in preterm infants with severe respiratory distress syndrome who require high levels of ventilator support and supplemental oxygen at 36 weeks postmenstrual age (PMA) [46,47]. In infants less than 26 weeks who are at highest risk for late PH to obtain DE sooner (between 30 to 60 days of life). And, in the setting of established BPD, preterm infants who at 36 weeks PMA who still require positive pressure ventilation support and have recurrent cyanotic episodes screening for PH is warranted at monthly intervals. A simple strategy would be to use echocardiograms to screen every patient at 36 weeks of age who is diagnosed with moderate or severe BPD, but how often PH would be missed in patients with milder BPD is uncertain.

The screening echocardiography should always assess for tricuspid regurgitation jet velocity, but what is of highest importance is: septal flattening, RV dilation, and other parameters of RV function.

Future Directions

Despite the overall decrease in BPD severity, dysregulated vascularization is a characteristic feature. Hence, due to the resultant higher vascular resistance, BPD-associated PH has strong biological rationale. The relatively common incidence therefore is not surprising. It may be speculated that the presence of PH in BPD is simply a marker of more severe BPD [27,48].

Echocardiogram remains recommended on all patients as the screening tool of choice, with follow up of cardiac catheterization. However, the markers of PH on ECHO vary

from quantitative assessment to qualitative assessments. Even the quantitative assessments of PH using tricuspid regurgitation jet velocity have been shown to have relatively poor correlation with cardiac catheterization. In view of these limitations of the screening tool itself, it is possible that BPD-associated PH remains under-diagnosed. However, without evidence of any benefit of earlier screening and treatment, such screening programs may be best suited in the context of properly designed prospective studies or in a registry.

Although it is well-accepted that cardiac catheterization is the gold-standard, it cannot be used as a screening tool. Or maybe it could? Large scale collection and analysis of data on patients' experiences and outcomes have become staples of successful health systems worldwide. The collection of standardized information on patients' diagnoses, care processes, and outcomes, enables systematic comparison and analysis across multiple sites. They facilitate public reporting, retrospective and prospective research, and service improvement.

One of the potential uses of a registry, made of multiple tertiary care centers, is that we can demonstrate that weight and size are no longer absolute contraindications to catheterization. It is imperative that an increased number of interventional cardiologists are ready to evaluate and diagnose these infants even earlier on the BPD process to perhaps avoid disease progression and/or to better understand the progression. This can only be accomplished if cardiologists get excited with this new research opportunity and plan multicenter trials. Until then, evaluation by cardiac catheterization should be performed for disease severity and confounding factors.

In the meantime, we recommend cardiac catheterization for patients with BPD who: 1) have persistent signs of severe cardiorespiratory disease or clinical deterioration not directly related to airways disease; 2) are suspected of having significant PH despite optimal management of their lung disease and associated morbidities; 3) are candidates for chronic PH drug therapy. The goals of cardiac catheterization are to: assess the severity of PH; exclude or document the severity of associated anatomic cardiac lesions; and to assess pulmonary vascular reactivity in patients who fail to respond to oxygen therapy alone.

Another possible use of the registry to understand the progression of the disease could be by creating 2 screening protocols and test it in different institutions using echocardiography, specifically looking for septal flattening, RV dilation, and other parameters of RV function in addition to possible tricuspid regurgitation jet velocity. These variables can be expressed in 3 categories mild, moderate and severe. In serial ECHOs, they will have to compare the previous ECHOs with the most recent one. These variables can be tested starting at 30 days of life in infants less than 26 weeks and repeated monthly. Maybe having less information but consistent, although qualitative, information will help delineate the preferred start point for screening and progression. Data are extremely limited regarding various phases of pulmonary hypertension in bronchopulmonary dysplasia, including its natural history and mechanisms that cause pulmonary hypertension or contribute to progressive disease.

Author Contributions

Drs. Cuevas Guamán and Dahm conceptualized and designed the report, drafted the initial manuscript, reviewed and revised the manuscript and approved the final manuscript as submitted.

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Conflict of Interest

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