Role of functional echocardiographic parameters in the diagnosis of bronchopulmonary dysplasia-associated pulmonary hypertension

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Abstract
Echocardiogram (echo) is a commonly used noninvasive modality for the diagnosis of bronchopulmonary dysplasia associated pulmonary hypertension (BPD-PH). Though not considered the gold standard for the diagnosis of BPD-PH, it is an extremely valuable tool in the neonatal and pediatric population, especially when cardiac catheterization is not feasible. In addition to the traditional echo parameters that are used to assess the presence of BPD-PH, much attention has been recently placed on newer bedside echo measures, the so-called functional echo parameters, to aid and assist in the diagnosis. This review article provides a brief introduction to BPD-PH, describes the pitfalls of traditional echo parameters and details the newer echo modalities currently available for the diagnosis of neonatal PH.

Introduction
Survival of the extremely preterm infants has increased with advances in neonatal/perinatal therapies. The reported incidence of extreme prematurity in the US was 1.38% out of a total of 52,302 births in 2018 [1]. Despite the widespread use of antenatal steroids for lung development, surfactant and gentle ventilatory strategies, bronchopulmonary dysplasia (BPD) remains the most common complication of prematurity affecting up to two-thirds of infants born at ≤29 weeks gestational age. “Classic BPD” was characterized by pulmonary fibrosis secondary to oxygen toxicity and volumetric/barometric trauma by mechanical ventilation [2, 3].

In the current era, “New BPD” is seen in extremely premature infants born at 24–28 weeks’ gestation. Compared to “Classic BPD”, “New BPD” is characterized by disordered pulmonary development [4, 5]. BPD associated PH (BPD-PH), defined as an increased pulmonary arterial pressure, complicates the postnatal course of premature infants. In extremely premature infants, BPD-PH is associated with poor outcomes with high morbidity and mortality [6]. The American Heart Association (AHA) and American Thoracic Society (ATS) recommend screening for BPD-PH in premature infants [7]. However, due to lack of consensus regarding the screening and diagnostic criteria of BPD-PH, the true incidence of BPD-PH is unknown. Awareness of the prevalence, risk factors, and time-sensitive mortality of BPD-PH will allow physicians to develop screening guidelines and preventive strategies.

This review focuses on the use of newer bedside echocardiographic (echo) measures, for the screening and diagnosis of BPD-PH in premature infants and highlights the practical limitations of using routine echo and cardiac catheterization as the gold standard.

Definition of pulmonary hypertension
The guidelines by the ATS/AHA on pediatric PH defined PH as a mean pulmonary artery pressure (mPAP) ≥25 mmHg at sea level with a pulmonary capillary wedge pressure <15 mm Hg and an indexed pulmonary vascular resistance (PVR) of >2 iWU in infants >3 months of age.
Timing of BPD-PH screening

In premature infants, lung injury leads to BPD-PH emphasizing the importance of early interventions prior to development of irreversible changes, which was also endorsed by the National Institute of Health [12] and has been demonstrated in animal models [13]. Even though the AHA/ATS recommend screening for BPD-PH in premature infants with BPD at 36 weeks PMA [7], recent studies have suggested benefits of early screening of premature infants for BPD-PH. Mourani et al. found 42% infants had early PH (diagnosed on day 7) and 14% late PH (at 36 weeks PMA) with early PH being a risk factor for late PH [5]. Infants with late PH had greater duration of oxygen therapy and increased mortality. Among infants diagnosed with BPD-PH after 2 months of age, only 2/3rd infants survived at 6 months and only half of infants survived 2 years after the diagnosis. These results suggest that even subtle early echo features of pulmonary vascular disease in the first week are risk factors for BPD-PH. A case series of premature infants with BPD-PH treated with sildenafil demonstrated no significant improvement in respiratory scores and echo findings when therapy was started after 36 weeks PMA [14]. In summary, the natural history of BPD-PH is unclear based on the current literature. Premature infants with BPD are at increased risk of developing BPD-PH and early screening for BPD-PH by echo may be helpful to find premature infants at risk of BPD-PH.

Assessment of BPD-PH

Echocardiogram

Introduction

An echo probe has piezoelectric crystals. An electric potential applied to such a crystal results in mechanical distortion causing the crystal to resonate producing ultrasonic waves. An ultrasound beam traveling through the body will have some of its energy reflected back to the transducer and some of its energy transmitted forward [15]. Two dimensional (2D) imaging allows structures to be viewed in real time in a cross-section of the heart [16]. The most common 2D views are the parasternal long axis, the parasternal short axis, and the apical four chamber view. The M-mode echo, which provides a one dimensional view, is used for fine measurements [16].

In echo, the velocity of moving structures is assessed by the Doppler principle [15]. Estimates of blood-flow velocity can be made by comparing the frequency change between the transmitted and reflected sound waves. The simplified Bernoulli equation is used to measure a pressure differential...
across an orifice: \( \Delta P = 4 \left( V_2^2 - V_1^2 \right) \) where \( V_1 \) = the velocity proximal to the obstruction and \( V_2 \) = the velocity distal to the obstruction \[15\].

The two most common types of doppler used in echo are the continuous wave (CW) and the pulse wave (PW) doppler \[16\]:

Continuous wave (CW) doppler: It measures velocity along the entire length of the ultrasound beam and not at a specific depth. It has range ambiguity but there is no theoretical limit to the maximal velocity that can be measured.

Pulse wave (PW) doppler: It is used to measure localized velocity values of turbulent flow.

In the neonatal population, echo is the most commonly used modality for the evaluation of BPD-PH to estimate PAP and RV function as it is noninvasive, portable, and can be performed at the bedside \[17\]. Echo is useful to estimate the severity and diagnosis of BPD-PH, guiding initiation of therapy with pulmonary vasodilators, monitoring the response to treatment provided and finally monitoring BPD-PH while weaning treatment. Echo should be considered in all patients who meet the criteria of moderate-severe BPD according to the NIH definition and should be performed as early in the course as possible to enable early initiation of therapy \[18\].

Traditionally, increased tricuspid regurgitant (TR) jet velocity, right to left shunt across the foramen ovale and flattening of the interventricular septum (IVS) were used to predict elevated RV pressures and in turn sPAP in the absence of right ventricular outflow tract obstruction \[14\] (Figs. 1, 2 and 3). TR jet velocity is the most commonly used echo parameter to measure RV systolic pressure (RVSP) by CW doppler. A TR jet velocity >2.5 m/s is suspicious for PH and further workup may be considered especially in a preterm infant at risk for BPD-PH \[19\]. However, the TR jet needs a reproducible holosystolic envelope and is subject to technical difficulties in obtaining the appropriate images. In addition, the TR jet doppler velocity envelope may be affected by the presence of pulmonary stenosis or a significant ventricular septal defect. Mourani et al. found that a reliable TR jet doppler envelope is found in only 61% of pediatric echoes \[20\].

The presence of a right to left or bidirectional shunt at the level of the foramen ovale is a surrogate marker of increased RV pressures \[21\]. Interventricular septal curvature is an alternative marker of RV pressure based on the alignment of IVS (Table 1). Normally, the IVS bows into the right ventricle during systole due to the left ventricular systolic pressure being higher than the RVSP. A rounded contour of the IVS is suggestive of infra-systemic pulmonary pressures whereas a flattened IVS during systole is seen with supra-systemic pulmonary pressures. A flattened IVS that bows into the left ventricle during systole is highly suggestive of elevated pulmonary artery pressures although such interpretation is subject to inter-observer variability \[22\].

Echo evaluation is limited by lack of standardized definitions, difficulty in estimating the pulmonary pressures when a TR jet is absent and the technical skill of the operator. Other limitations include poor correlation between echo findings and cardiac catheterization in both adults and infants with PH \[23, 24\]. Fisher et al. compared echo findings performed during cardiac catheterization in 25 children under the age of two years and showed that echo was able to diagnose PH in 79% and to determine the severity in only 47% of cases \[24\].

The definitive diagnosis of PH is usually made by measuring the mPAP during cardiac catheterization, which

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Fig. 1 Figure showing tricuspid regurgitant jet velocity in a patient with severe pulmonary hypertension. The measured tricuspid regurgitant jet velocity is 5 m/s (-sign) which translates to an estimated right ventricular systolic pressure of 100 mmHg – right atrial pressure.
allows for vasoreactivity testing to determine responsiveness to oxygen and other pulmonary vasodilators such as inhaled nitric oxide. However, invasive procedures, anesthesia, and exposure to ionizing radiation must be carefully considered in sick infants and cardiac catheterization is not always practical [17]. Hence, other noninvasive methods of identifying PH in this population have been proposed. As an alternative to routine echo with measurement of TR jet, IVS alignment and inter-atrial shunting, functional echo parameters can also be used for the estimation of PAP.

Fig. 2 Subcostal coronal view in a patient with severe pulmonary hypertension. There is right to left shunting across a patent foramen ovale (blue flow, arrow).

Fig. 3 Parasternal short axis view in a patient with severe pulmonary hypertension. There is severe systolic interventricular septal flattening (arrow).

Table 1 Estimation of right ventricular systolic pressure based on left ventricular configuration.

| Left ventricular configuration | Estimated right ventricular pressure |
|-------------------------------|-------------------------------------|
| O-shaped LV*                  | <50% of LVP*                        |
| D-shaped LV*                  | 50–100% of LVP*                     |
| Crescent-shaped LV*           | ≥100% of LVP* (supra systemic pressure) |

LV left ventricle.
LVP left ventricular pressure.
In this manuscript, we define functional echo parameters as the newer echo modalities that are available for the screening and diagnosis of PH, which strays from the traditional parameters of TR jet velocity, IVS alignment, and inter-atrial shunting. In the context of BPD-PH, RV function assessment is crucial. The principal manifestations of RV dysfunction in infants with BPD-PH are a triad of changes in RV configuration (dilation and hypertrophy of RV), right to left interaction (IVS shifting) and RV systolic dysfunction. However, assessment of RV function is extremely challenging by echo, and IVS alignment is subject to inter-observer variability. In infants at high risk of BPD-PH, serial functional echoes can be used for risk stratification, diagnosis, estimation of severity, and monitoring the response to treatment of BPD-PH.

**Hemodynamic assessment of RV**

**Estimation of pulmonary artery pressure (PAP)**

**Systolic PAP**

The estimation of the sPAP is traditionally based on the peak velocity of the TR jet. The simplified Bernoulli equation using CW doppler to assess the TR jet describes the relationship of TR and RVSP as a surrogate of sPAP in the absence of RV outflow tract obstruction [25]. RVSP may be underestimated by TR jet assessment in cases with moderate to severe TR and also because of a suboptimal doppler spectral envelope. In addition, overestimation of RVSP may occur if there is pulmonary valve stenosis. So although a complete TR jet envelope may provide an accurate estimation of sPAP, care should be taken to ensure that there is no RV outflow tract obstruction and the doppler envelope does not represent another lesion such as a ventricular septal defect.

**Mean PAP and diastolic PAP**

A pulmonary regurgitation (PR) signal is obtained in the parasternal short-axis view. Mean PAP and diastolic PAP (dPAP) can be estimated from the early-diastolic and end-diastolic PR velocity respectively, using the simplified Bernoulli equation [26] (Fig. 4). A limitation of mPAP and dPAP estimations is that the PR signal may be poor [23]. An overestimation of the right atrial pressure and the use of inadequate doppler signals are also identified as frequent pitfalls [24].

**Left ventricular systolic eccentricity index (LV-sEI)**

Another objective way of estimating PAP is by calculating the LV-sEI. LV-sEI is the ratio of LV dimensions parallel and perpendicular to the IVS. LV-sEI is measured in the short axis parasternal view (Fig. 5). It is defined as the ratio of D2:D1 where D1 is the LV short-axis diameter perpendicular to the septum and D2 is the left ventricle short-axis diameter parallel to the septum. Normal LV-sEI ratio is 1 and it increases in BPD-PH with a value >1 suspicious for BPD-PH in a preterm infant [19]. LV-sEI allows
quantification of subjective IVS flattening. Revanna et al. found that LV-sEI was significantly higher in infants with BPD-PH [27]. A recent study of a prospectively enrolled cohort at high risk for BPD showed that the sEI was the only objective parameter among the evaluated assessments of RV mechanics that was independently associated with BPD severity at 36 weeks PMA [28]. The sEI is highly reproducible and is independent of the angle of insonation. The sEI reflects interventricular interactions, with changes in sEI driven by perturbations of RV/LV pressures [28].

### Pulmonary artery acceleration time (PAAT)

Pulmonary artery acceleration time (PAAT) is the interval (in ms) from the onset of ejection to the peak flow velocity and may be used for the assessment of PVR (Fig. 6). PAAT is a validated noninvasive, feasible, and reproducible echo modality to measure PVR in BPD-PH [29]. Healthy controls without PH have PAAT > 120 ms [30]. PAAT < 90 ms reliably detects high PAP whereas a value <40 ms suggests severe PAP. A PAAT < 70 ms in a preterm infant is highly suggestive of elevated PVR and potential BPD-PH [19]. In adults at risk for PH, a PAAT < 100 ms indicates a high probability of increased PAP [31]. The normal PW doppler profile in the right ventricular outflow tract is smooth, parabolic, and without “notching” of the doppler envelope with a notch suggestive of elevated PVR [32].

### Right ventricular ejection time (RVET) and PAAT:RVET

RVET is the time interval between the onset and cessation of systolic flow with PAAT:RVET being inversely related to PAP during cardiac catheterization [33]. PAAT:RVET ratio has high sensitivity and specificity in detecting the triad of elevated PVR, decreased pulmonary arterial compliance, and RV dysfunction [29]. In the pediatric population, patients without PH usually have PAAT:RVET ≥ 0.31 while a PAAT < 90 ms and PAAT:RVET < 0.31 reliably detect elevated PVR with a sensitivity and specificity > 90% [29]. Since absolute PAAT values are heart rate dependent; the PAAT:RVET is proposed to correct for the shortening of ejection at higher heart rates [34]. Kosturakis et al. found that even though PAAT and RVET shorten with increasing heart rate, the ratio of PAAT:RVET remains unchanged [33].

### Global and regional functional assessment of the RV

#### RV longitudinal systolic function (Tricuspid annular plane systolic excursion—TAPSE)

The tricuspid annular plane systolic excursion (TAPSE) reflects longitudinal excursion of the tricuspid annulus toward the apex and is measured by M-mode from the 4-chamber view [35, 36] (Fig. 7). It measures the distance of systolic excursion of the tricuspid annulus which has a good correlation with RV global systolic function. Although TAPSE is reproducible and simple to measure, accurate measurement depends on the angle of the echo probe and preload [37]. Reference values of TAPSE measurements in adults, pediatric, term, and premature infants range are available [38–40] with reduced TAPSE values having a high specificity for RV dysfunction [41]. With sustained PH
over years in children and young adults, TAPSE values decrease [42]. In a prospective study of children with PH, treatment-induced changes in TAPSE were associated with improved survival [43]. A TAPSE z score < −3 in a preterm infant is highly suspicious for BPD-PH [19]. TAPSE significantly improves after initiation of PH therapy in pediatric patients and may be used to monitor the response to PH therapy [44]. However, it must be remembered that TAPSE does not take into account segmental RV dysfunction.

**RV fractional area change**

The RV fractional area change (FAC), representing the ratio of systolic area to diastolic area, is a commonly used index of RV contractility. RV FAC is less reproducible than TAPSE but accounts for apical, basal, radial, and longitudinal function [41]. In a recent pediatric PH study, RV FAC correlated with indexed RV stroke work and TAPSE [45]. Studies in the neonatal literature have suggested that a
number less than 30% is abnormal and suggests diminished RV function [46]. Combining RV FAC with other parameters for the assessment of RV function may allow a more comprehensive assessment of children with PH. A limitation of this method is that the RV FAC is dependent on preload.

**Deformation imaging (RV strain and strain rate)**

Deformation imaging is used to assess global and regional myocardial function (Fig. 8). It allows for direct assessment of myocardial muscle fiber shortening and lengthening throughout the cardiac cycle via strain and strain rate [47]. RV global longitudinal peak systolic strain and strain rate were significantly affected in adults with PH, and studies have shown that strain and strain rate correlate with invasive and non-invasive markers of PH [48, 49]. In a small pediatric PH study, strain was found to be an earlier predictor of RV dysfunction [50]. A recent study in neonates with BPD-PH has suggested that an RV peak longitudinal strain greater than −14 is a discriminative marker of BPD-PH [51]. The limitations of strain and strain rate measurements are the relatively low temporal solution of 2D speckle tracking in the presence of high heart rates and the long post-processing times [25].

**Tissue doppler**

Tissue doppler velocities may be used to assess regional myocardial function [25] (Fig. 9). Tissue doppler velocities are dependent on geometry, which has implications in children with congenital heart disease, who have variable RV size, mass, and geometry [52]. In adults, tissue doppler indices measurements have been shown to have a specificity of 100% to identify patients with precapillary PH [53]. Pediatric PH patients had lower systolic ($S'$) and early-diastolic ($E'$) velocities at the lateral tricuspid, septal, and lateral mitral walls [54]. In addition, RV tissue doppler indices have been found to correlate well with invasive pulmonary hemodynamics in pediatric patients with PH [55]. Currently, there are no validated tissue doppler values for the diagnosis of BPD-PH in neonates. The limitations of tissue doppler indices are predominantly related to dependence on preload, dependency on heart size, and the angle of interrogation.

**Myocardial performance index (Tei index)**

The Tei index evaluates global ventricular function by measuring the ratio of isovolumic contraction and relaxation time intervals to ventricular ejection [56] (Fig. 10). This is obtained via tissue doppler on the RV free wall and a PW doppler near the tricuspid annulus [23]. Isovolumetric contraction time, isovolumetric relaxation time, and ejection time of the RV are then measured. The longer the isovolumetric phases, the higher the Tei index and the worse the RV performance. The RV Tei index correlates well with right heart catheterization parameters [57, 58]. In a recent study, neonates with BPD-PH had a higher mean MPI as compared to those without PH (0.46 ± 0.16 vs 0.34 ± 0.21).
although absolute cut-off values are lacking in this population [59]. Advantages of the Tei index are that it is a combined ventricular-vascular index and can be measured independent of ventricular geometry. Its limitations include the inability to allow distinction between systolic and diastolic dysfunction.

**3D echo**

3D echo provides significant advantages for measurement of RV size, mass, and ejection fraction [60] (Figure. 11). Studies have demonstrated consistency in RV mass and volume measurements by 3D echo and cardiac MRI [61]. Kong et al. reported that regional and global RV systolic dysfunction in adult PH patients measured by 3D echo was inversely related to the PAP and PVR [62]. In adults with PH, good correlation was found in the calculation of RV ejection fraction and RV end-diastolic-volume determined by either 3D echo or magnetic resonance imaging measurements [63]. Although studies in the pediatric population are limited, one study showed that pediatric PH patients have impaired RV function, RV volumes, and FAC by 3D echo [64].
Cardiac catheterization

While the gold standard for the diagnosis of BPD-PH is cardiac catheterization, it is an invasive procedure and the risks and benefits must be weighed especially in the fragile neonatal population. The advantages of cardiac catheterization include direct measurement of PAP and PVR, assessment of the contribution of anatomic shunts, detection of left ventricular diastolic dysfunction, and the diagnosis of pulmonary vein stenosis [65]. This procedure in addition to being diagnostic, allows interventions to be performed. Furthermore, cardiac catheterization permits performance of vasoreactivity testing. A positive vasoreactivity test in patients with idiopathic PH can identify patients with a more favorable long-term prognosis and predict response to calcium channel blockers [66]. A recent study focusing specifically on patients with BPD-PH demonstrated that positive vasoreactivity testing during cardiac catheterization is associated with decreased mortality [10]. The need for cardiac catheterization should be weighed on a case-by-case basis but there are certain indications in which the benefit may outweigh the risk of this invasive procedure. These include assessment of patients with BPD and severe PH by echo for assessment of left ventricular diastolic dysfunction, pulmonary vein stenosis, and anatomic shunt lesions and those patients whose PH fails to improve with optimization of respiratory status or initiation of medical therapy [65]. In addition, assessment of vasoreactivity testing may provide useful prognostic information regarding the severity of pulmonary vascular disease and BPD [65]. While the latest guidelines suggest that every patient with idiopathic PH attempt to undergo cardiac catheterization and vasoreactivity testing, there are no clear guidelines for the BPD-PH population specifically [9]. The guidelines also state that in those cases where the suspicion of PH is high by noninvasive imaging and the patient is too sick to undergo cardiac catheterization, PH therapy may be initiated cautiously [9]. In these cases, catheterization remains a useful tool to serially follow PH patients who are already on medical therapy.

Conclusion

Despite improved neonatal management, BPD and BPD-PH is common in extremely premature infants and have a high incidence of morbidity and mortality. The AHA/ATS recommend screening for BPD-PH in premature infants with BPD at 36 weeks PMA, however, studies have demonstrated that irreversible changes may have occurred by that time. Noninvasive diagnosis of PH by echo has received increased attention recently with newer modalities and improved technology aiding in the diagnosis. However, no single noninvasive modality provides a complete assessment and diagnosis of PH and its associated effects on the RV. Early detection and management of BPD-PH may improve the outcomes of extremely premature infants. We suggest all premature infants with BPD should be screened prior to 36 weeks PMA for BPD-PH by functional echo. Functional echo should include LV-sEI, PAAT, TAPSE, RV FAC, strain imaging, tissue doppler, Tei index in addition to the routine echo parameters of TR jet velocity and assessment of the IVS curvature during systole.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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