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Echocardiography

Echocardiographic Assessment of Pulmonary Hypertension in Infants with Bronchopulmonary Dysplasia: Systematic Review of Literature and a Proposed Algorithm for Assessment

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Background: As survival and outcomes continue to improve in neonates born prematurely, there is an increasing need to promptly identify and treat pulmonary hypertension (PHT) in this population. Several echocardiographic indices have been used to evaluate for PHT. There is no clear consensus on how to utilize these parameters specifically for the evaluation of PHT in infants with chronic lung disease of prematurity. Objectives: The objectives of the study were (1) to identify the different echocardiographic techniques for assessment of PHT in infants with chronic lung disease of prematurity in an evidence-based manner and (2) to establish an echocardiographic screening protocol based on available literature using different echocardiographic techniques. Methods: We conducted a systematic review of the literature regarding use of echocardiographic techniques for evaluation of PHT in infants with bronchopulmonary dysplasia. On the basis of the available evidence, we came up with a screening algorithm using various echocardiographic techniques. Results: We identified nine techniques that had been employed for detection of PHT noninvasively using echocardiography in 23 studies. Using these echocardiographic parameters, we came up with a flow chart to diagnose PHT in infants born prematurely, based on presence or absence of tricuspid regurgitation, presence or absence of patent ductus arteriosus, and direction of flow. Conclusions: We have proposed a new screening strategy for assessment of PHT using echocardiography in infants with chronic lung disease of prematurity. Further studies will be necessary to confirm its validity. (Echocardiography 2015;32:819–833)

Key words: bronchopulmonary dysplasia, prematurity, pulmonary hypertension, screening, echocardiography, chronic lung disease

Pulmonary hypertension (PHT) is a significant comorbidity in infants with bronchopulmonary dysplasia (BPD). As survival and outcomes continue to improve in neonates born prematurely, there is an increasing need to monitor and screen for these additional comorbidities for their early diagnosis and treatment. Since echocardiography is an important tool in the assessment of patients with PHT, its role as a screening tool in patients with BPD is not clearly known.

BPD is classified into grades of severity on the basis of need for supplemental O_2 and/or mechanical ventilatory support at 28 days of life or 36 completed weeks.[1] For most infants with mild BPD, their clinical course is relatively benign and PHT is far less common. The group of infants with moderate-to-severe BPD is the one that requires close attention. These infants tend to have high rate of morbidity primarily due to their limited pulmonary reserve and higher chances of having PHT as a consequence of their severe lung disease.

Several echocardiographic indices have been used to identify and characterize the severity of PHT in BPD.[2] However, there are technical challenges in obtaining adequate echocardiographic studies in young infants and toddlers. Lack of tricuspid regurgitation (TR) jet may lead to inadequate assessment of pulmonary vascular pressures. Several studies have looked at additional echocardiographic measurements that can be used for assessment of right ventricle (RV) or pulmonary artery (PA) pressures. There is no clear consensus on how to utilize these parameters and in what specific situations can these

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parameters be considered useful. We have extensively reviewed the literature regarding use of echocardiography in evaluation of infants with BPD and have devised an algorithm for the assessment of PHT in these patients.

Methods:

The primary aim of this study was to examine the evidence supporting the use of a screening protocol for PHT in premature neonates with chronic lung disease of prematurity. We searched several electronic databases (PubMed/MEDLINE, Scopus, Cochrane Library, CINAHL [EBSCO Host], Web of Science) using a predefined search strategy to identify the relevant studies. The following search terms were used in our search strategy: “PHT,” “echocardiography,” “chronic lung disease of prematurity,” “BPD,” “diagnosis,” “screening,” and “systematic review.” The search methodology and the results obtained have been summarized in a separate online supplement. Inclusion criteria included neonatal and pediatric studies (retrospective or prospective case series, case–control studies, or intervention studies) that reported the use of echocardiographic techniques for assessment of PHT. Studies were excluded if they were done in animal models, described an adult patient population, discussed only risk factors for development of PHT, were related to other cardiovascular or lung anomalies (such as congenital heart disorders or congenital diaphragmatic hernia), or if they did not have any echocardiography parameters included. All studies evaluating the use of echocardiography in the diagnosis of PHT were included and then screened individually by the authors. We also searched the bibliographies of the selected studies to identify additional studies that may have been overlooked in our initial search. If the study population comprised infants and children born prematurely, then those studies were included in our review and the rest were excluded. Within the selected studies, further categorization was made using the type of echocardiographic parameters being assessed.

Results:

A total of 120 citations were initially identified based on our predefined search criteria (Fig. 1). We excluded 35 studies, as they were review articles, 32 studies performed in older age groups and 17 studies that were concerned mainly with risk factors. Further screening of the remaining 36 manuscripts led to the exclusion of another 13 manuscripts that either did not satisfy our inclusion criteria or had one of the exclusion criteria. A total of 23 studies that met our inclusion and exclusion criteria were finally selected (Table I). All the selected studies were either prospective or retrospective case series or case–control studies of infants with BPD who underwent echocardiographic assessment for PHT. About half of the included studies (13/27) had control subjects. There were 2 studies that attempted to classify patients into groups based on the severity of their BPD, while another 2 studies utilized pulmonary vascular resistance (PVR) measurements to categorize the subgroups. From these studies, we identified 9 techniques that had been employed for detection of PHT noninvasively using echocardiography. These techniques included tricuspid regurgitation jet velocity (TRJV), systolic duration to diastolic duration ratio, tricuspid valve regurgitation to velocity tissue integral, dynamic compliance, pulmonary artery capacitance (PAC), pulmonary flow analysis, septal flattening, tissue Doppler study, and tricuspid systolic motion (TSm).

Studies of Echocardiography Parameters:

Echocardiography is a widely available modality that can be used as a screening tool for the assessment of PHT in infants with BPD. The conventional measurements on echocardiography may not be able to reliably detect PHT. This was elegantly showed by Mourani et al.[3] as they compared the echocardiogram assessments of PHT in infants with BPD with subsequent cardiac catheterization-based measurements of pulmonary artery pressure (PAP). Systolic PAP (sPAP) could be estimated in only 61% (TRJV) of echocardiography studies, and there was poor correlation between echocardiogram and cardiac catheterization measures of sPAP in these BPD infants. Tricuspid valve regurgitation peak velocity is usually difficult and may not be reliable in BPD patients due to associated pulmonary hyperinflation and alteration of cardiac position.[4] All the studies that we reviewed regarding the use of echocardiography to assess PHT in BPD infants were divided into two main categories, depending on presence or absence of TR jet.

Tricuspid Regurgitation Jet Studies:

TR jet: TR jet dependent studies correlated pulmonary pressure to crude tricuspid regurgitation peak velocity. Benatar,[5] Skinner et al.,[6] Mourani et al.,[7] Roushdy et al.,[8] and Stuart et al.[9] showed correlation ranging between 0.19 up to 0.95; with the incidence of regurgitation detection ranging between 14% and 80%.[10]

Systolic to diastolic time ratio: TR jet has been used to acquire ratio of systolic time to diastolic time to predict pulmonary pressure in infants with congenital diaphragmatic hernia. Aggarwal et al.[11] showed reliable TR jet in 83% of these

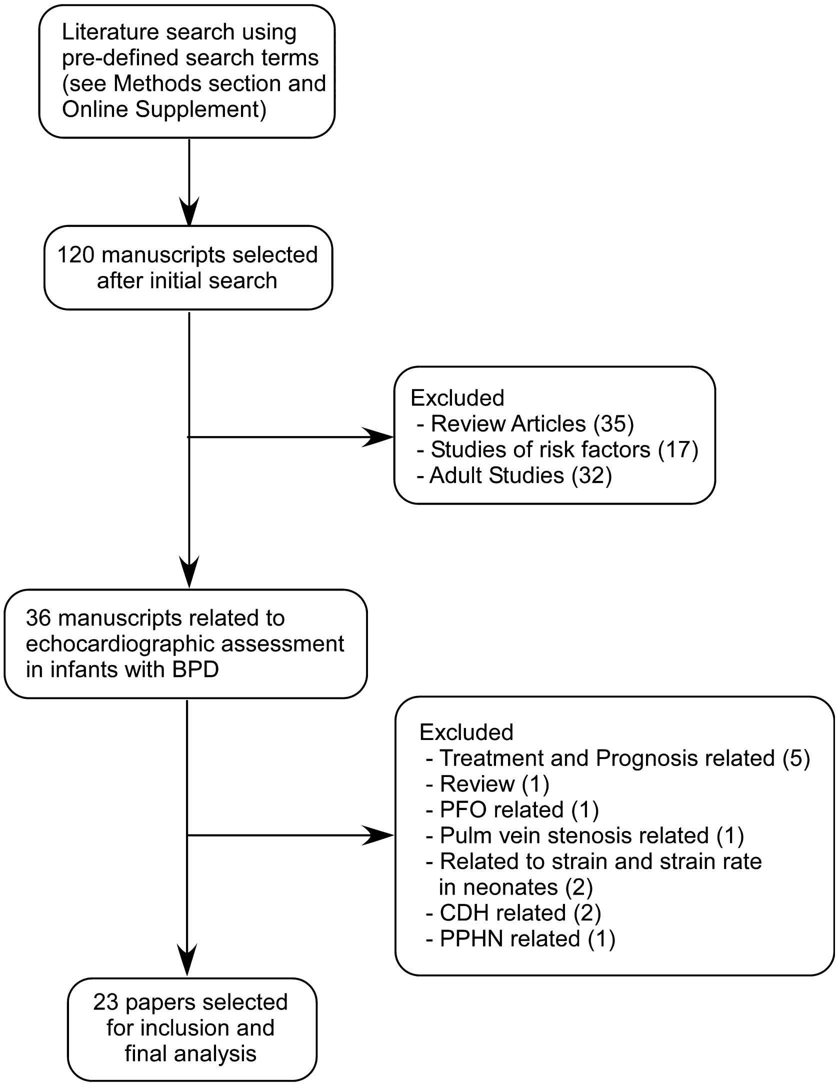

Figure 1. Search results for systematic review of literature.

patients, though the SD/DD was measurable in only 45%. The diastolic duration was significantly shorter than that of control subjects ($P < 0.0001$), and the SD/DD ratio was significantly higher than that of control subjects as well ($P < 0.0001$). Similarly, Alkon et al.[12] showed the S:D ratio was significantly higher in patients with PHT than in controls (1.38 ± 0.61 vs. 0.72 ± 0.16, $P < 0.001$).

TRV/VTI (velocity time integral) ratio: Ajami et al.[13] used ratio between TR velocity and tissue velocity integral (TRV/VTIm) of the pulmonary valve Doppler. The authors showed good correlation of this parameter with the PVR measured by cardiac catheterization ($R^2 = 0.53$; $P = 0.008$), having a sensitivity of 71.4% and specificity of 90% for a PVR >6 Wood Units (WU).

Dynamic compliance (Cdyn): Dyer et al.[14] used TR velocity to measure dynamic compliance that showed lower peak wall velocity values and lower Cdyn values in PHT patients than control subjects ($P < 0.01$).

Pulmonary artery capacitance: Friedberg et al.[15] used TR velocity to calculate PAC, which correlated well with values obtained by cardiac catheterization ($r = 0.74$, $P < 0.0001$). PAC also correlated with RV anterior wall thickness, which can be a surrogate for RV work.

Non-TR Jet Studies:

There are several neonatal studies that did not use TRJV to assess PHT. These have been classified as follows:

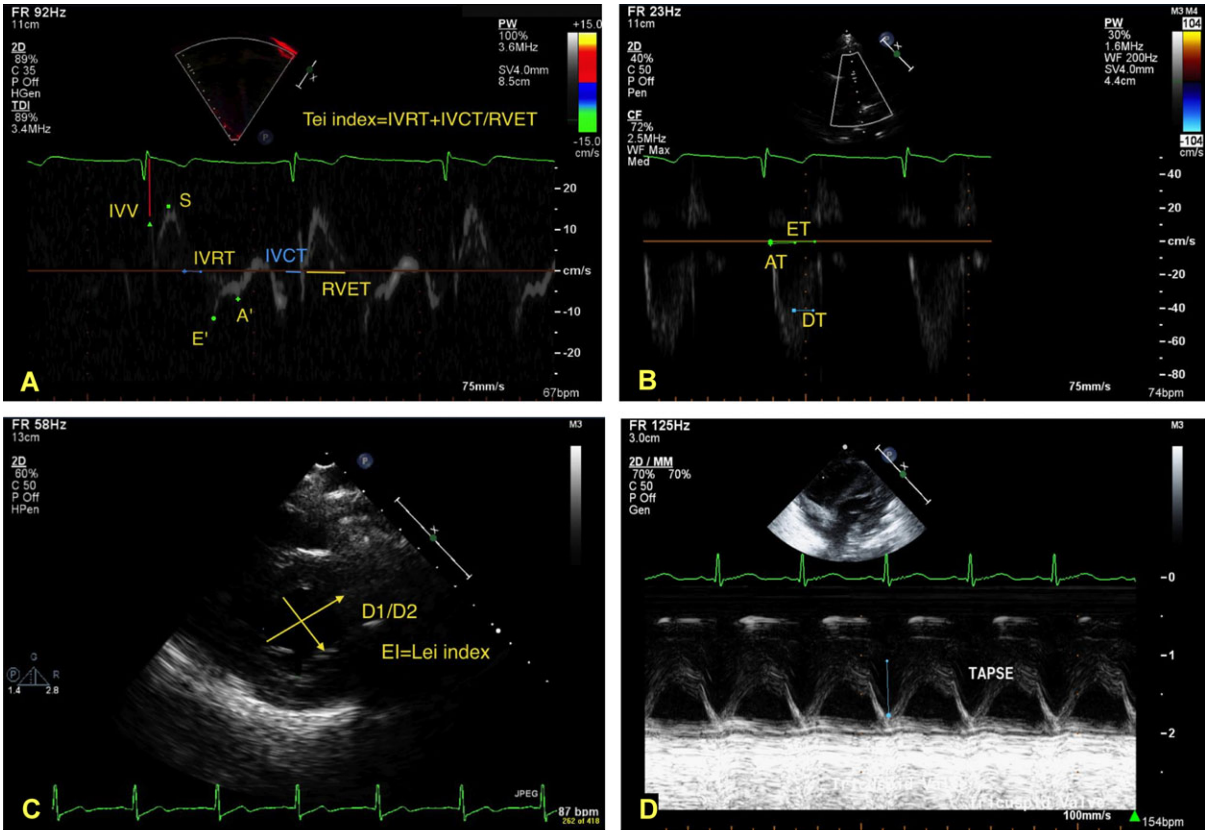

Figure 2. Echocardiography parameters used for assessment of pulmonary hypertension. **A.** TDI and Tei index calculation. **B.** Pulmonary artery flow analysis. **C.** Eccentricity index calculation (Lei index). **D.** Measurement of TAPSE.

I. Quantitative studies that assessed different indices in Doppler pulmonary flow,
II. Tissue Doppler image (TDI) studies, or
III. Qualitative assessment of right atrium, right ventricle, and pulmonary artery diameters.

Quantitative studies: ***AcT/RVET:*** Measurement of the ratio between acceleration time (measured or corrected) and right ventricle ejection time (AcT/RVET) (Fig. 2B) has been shown to be inversely correlated with PAP in adults. This measurement was also used in multiple studies done in younger patients: Subhedar and Shaw,[16] Evans and Archer,[17] Benatar,[5] Murase and Ishida,[18] Cevik et al.,[19] Cooper et al.,[20] Sehgal et al.,[10] Fitzgerald et al.,[21] and Fuoron et al.,[22] made similar ratio but he calculated right preejection time (RPET) and right ejection time (RET) ratio by M mode instead of Doppler.

Cevik, Benatar, and Fitzgerald showed that there is a negative correlation between AcT/RVET versus PAP and PVR index (RPI). They also showed that AcT/RVET can differentiate vasoactive PHT from the nonvasoactive group in 100% FiO_2. A cutoff value of AcT/RVET of less than 0.31 is considered diagnostic of PHT. Subhedar and Fuoron showed negative correlation between ratio and duration of oxygen treatment and worse chest x-ray finding for BPD.

Inflection time and deceleration time: Inflection time (InT) and deceleration time (DT) are pulmonary flow velocity measurements that can be corrected for the heart rate dependence by dividing the measured values by the square root of the interval between onset of ejection (Fig. 3A). Cevik et al.[19] and Nakahata et al.[23] studied InT and DT, while Roushdy et al.[8] studied only InT in PHT patients. Both indices can differentiate PHT patients from control and may also differentiate PHT oxygen responders versus nonresponders, as well as low-PVR versus high-PVR patients. Nakahata et al. also suggested that left pulmonary artery flow Doppler study is more accurate than main pulmonary or right pulmonary arteries.

Based on their data, both Nakahata et al. and Roushdy et al. suggested that InT of 6 could be used as a cutoff value to differentiate responders versus nonresponders as well as to differentiate high- and low-PVR groups (<6 WU/m^2 by catheterization).

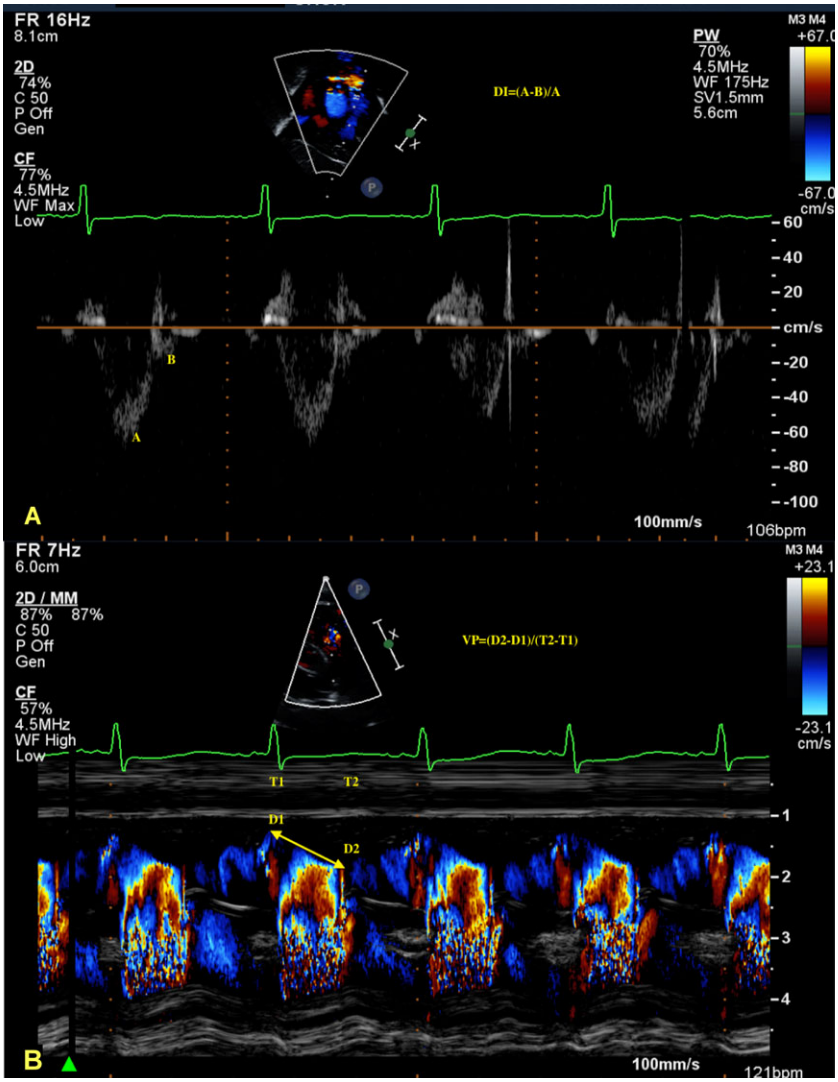

Figure 3. Echocardiography images showing the assessment of deceleration index and velocity propagation. **A.** Deceleration index, which is the ratio of the difference between inflection flow and peak flow to the peak flow. **B.** Velocity propagation, which is the ratio of the difference between two distances to the difference between the 2 time points.

Velocity propagation: Velocity propagation is based on the principle that changes in the local pressures due to changes in pulse propagation wave speed will affect the velocity of blood as well (Fig. 3B). It is measured on the color M-mode trace of flow in PA by the tracking of fluid moving at a constant velocity. Shandas et al.[24] found colored M-mode Doppler-derived velocity propagation (Vel_{prop}) correlates better to PVR ($R = 0.87$) than to pressure ($R = 0.73$).

Tricuspid annular plane systolic excursion: Tricuspid annular plane systolic excursion (TAPSE) is a simple echocardiographic measure of RV ejection fraction that is measured by evaluating the systolic excursion of the lateral tricuspid annulus that provides an estimate of longitudinal myocardial shortening (Fig. 2D). TAPSE has been evaluated in adults with PHT and was also studied in preterm infants by Koestenberger et al.[25] It was suggested by adult studies that lower TAPSE values occur with PHT. Since TAPSE values increase in a linear fashion from the 26th week to the 41st week of gestation, it can be used as a measure of RV function in preterm neonates. Based on normative data from Koestenberger et al., TAPSE values less than 0.5 cm (which is the −2 SD from normal in preterm less than 30 weeks gestational age) can be used to identify PHT in this group of patients.[25]

Tissue Doppler studies: ***Tissue pulse Doppler:*** Tissue Doppler imaging (TDI) is a novel way of using Doppler technique by interrogating a point on the myocardium rather than blood flow (Fig. 2A). By using a consistent point of reference, TDI has shown good correlation with cardiac catheterization-based data regarding RV and LV function. Yates et al.[26] showed linear correlation between BPD category and RV-E/E′ (P = 0.07). They found significant differences in RV-E/E′ between mild versus moderate BPD and also between mild versus severe BPD (P = 0.03 and 0.004, respectively). Patel et al.[27] showed RV-E, RV-S, RV-IVV (isovolemic velocity) and RV-E′ were significantly lower in PHT versus control (P values <0.0001, 0.0001, 0.001, and 0.0001, respectively). Septal E′ was significantly lower in PHT patients than control with P-value <0.001. Akcan et al.[28] showed TVE and different sites of E′ measurements (TV-E/E′ medial, TV-E/E′ lateral, and RV-E/E′) can differentiate BPD from control. Also it can differentiate different severity of BPD.

Roushdy et al.[8] showed that a TSm velocity cutoff value of 6.16 cm/sec provided the highest balanced sensitivity (85.7%) and specificity (66.7%) to accurately estimate catheter-based PVR >6 WU/m^2. A cutoff value less than 7.62 cm/sec had 100% specificity to predict PVR >6 WU/m^2. Also there was significant negative correlation between the TSm studied and invasive measurement of PVR (r = 0.511 and P value = 0.0002).

Tei index (myocardial performance index [MPI]): Tei index is a measure of global ventricular function that is calculated on echocardiography by dividing the sum of isovolumic contraction and relaxation times with the ejection time.[29] Akcan showed lower IVRT (isovolemic relaxation time) in control versus BPD (P = 0.001). Patel et al.[30] showed RVMPI was significantly elevated in the PHT group (P < 0.0001) with poor correlation (R^2 = 0.05; P = 0.17).

Qualitative studies: ***Right heart dimensions:*** Mourani et al.[3] studied correlation between PHT in infants and children with BPD and their right heart qualitative indices measured by echocardiography. Septal flattening (which occurred in 84% of cases) showed higher sensitivity of 88% followed by right ventricular dilatation (84%), while the highest specificity was noted for right ventricular hypertrophy (83%). The least sensitive and least specific parameter was pulmonary artery dilatation. The performance of these qualitative measures of right heart function was noted to be better in echocardiograms where a TR jet could be found, thus limiting their usefulness when TR jet is not present.

Septal flattening (eccentricity index) (Fig. 2C): King et al.[31] studied reciprocal normalized radius of curvature (modified later on as eccentricity index) for children in control group versus 2 groups of PHT (first group RVP <50% systemic pressure and second one RVP >50% systemic pressure). Aggarwal et al.[32] showed that an eccentricity index of less than 0.81 could differentiate PHT in congenital diaphragmatic hernia from control subjects. Also, del Cerro et al.[33] reported the use of interventricular septal (IVS) morphology if TR was not quantifiable. In their study, PHT was diagnosed on the basis of end-systolic flattening of IVS, with or without RV dilatation, using the different patterns (first described by King et al.). This parameter also showed improvement with older age and with treatment in their cohort.

List of Indices that Could Be Included in Echocardiographic Study for Infants with BPD:
In the presence of TR:

- Tricuspid valve jet velocity (pulmonary systolic pressure) >40 mmHg.
- Ratio of systolic time to diastolic time (SD/DD) >1.15.
- Ratio of tricuspid valve regurgitation to velocity time integral (TVR/VTI) >0.14.

With absent TR jet (Table II):

- Tissue Doppler:

  a Pulse: RV-IVV <5.2 cm/sec, RV-S (TSM) <7.6 cm/sec, and RV-E′ less than −4.3 cm/sec.
  b MPI >0.38

- TAPSE <0.5 cm
- Left pulmonary artery flow analysis unless PDA flow happens to occur right to left.

  a InTc <4.3 msec
  b AT/RVET <0.31
  c Deceleration index >0.4

- Eccentricity index of right ventricle (Lei index): <0.81.

Synthesis of an Echocardiographic Screening Protocol:
On the basis of the review of the abovementioned studies, we have synthesized a screening protocol for PHT in infants and toddlers with BPD, which utilizes these echocardiographic parameters in an evidence-based manner (Fig. 4). In the presence of TR with good regurgitant

TABLE I

Different Studies that Utilized Echocardiography Parameters to Screen for PHT in Neonates and Infants with Bronchopulmonary Dysplasia

Reference	Study Type	Number of Subjects	Age	Echo Parameters	Significant Outcome
Murase and Ishida[18]	Prospective	84 total (64 BPD)	<28 days	AcT/RVETc	• AcT/RVETc for control was higher than BPD with $P < 0.001$ at 12 hours of life. • AcT: RVET(c) of VLBW with GA >30 weeks showed increase during first 48 hours of life vs. <30 weeks showed increase after day 14.
Mourani et al.[3]	Retrospective	25	<2 years	TRJV RVD Septal flattening	• TR jet occurred in 61%. • sPAP >40 mmHg by echo has sensitivity 88% with specificity 33%. • Qualitative measures have low sensitivity; RVD and septal flattening are highest, 67% each. • Two qualitative or more increased sensitivity to 86% (100% with TRJV).
Benatar [5]	Prospective	42	3–17 weeks	TVR AT/ET	• TR jet happened to be 44%. • AT/ET showed correlation with TR.
Skinner et al.[6]	Prospective	26	<1 year		• TR jet correlated with catheter measurements ($r = 0.95$). • Doppler values tended to underestimate RV pressure with clinically nonsignificant value of about 2 mmHg.
Roushdy et al.[8]	Prospective	175 PHT patients	0.4–18 years	TSm TRV/TVI AcT	• Both the TRV and TSm are correlated with cath measurement of PVR with $r = -0.51$, $P = 0.0002$ and $r = 0.38$ with $P = 0.006$, respectively. • TSm cutoff value of <16.16 cm/sec or TRV cutoff value of >3.96 m/sec with high sensitivity and specificity to determine PVRcath >6.31 in patients WU/m^2. • TRV/TVI correlated with invasive PVR ($r = 0.347$ and $P = 0.015$), with cutoff value >0.149 and a cutoff value for the AcTc of <4.34.
Alkon et al.[12]	Retrospective	47 PHT vs. 47 controls	Less than 19 years old	RV SD/DD	• The S:D ratio was significantly higher in patients than in controls (1.38 ± 0.61 vs. 0.72 ± 0.16, $P < 0.001$).

(continued)

Table I Continued

Reference	Study Type	Number of Subjects	Age	Echo Parameters	Significant Outcome
Ajami et al.[13]	Prospective	20 patients	1–30 years	TRV/VTI_{RVO}	• TRV/VTI correlated linearly with cath-derived PVR in patients with CHD and PHT (independent of age, BSA, or RVOT diameter ($R^2 = 0.562$, $P = 0.008$). • TRV/VTI value of 0.2 provides a sensitivity of 71.4% and a specificity of 100% for PVR = 6 WU and a sensitivity of 90% and specificity of 90% for PVR = 8 WU. • Echo-derived PVR can be calculated with following equation: (PVR = 31.87 [TRV/VTI_m] + 2.7).
Dyer et al.[14]	Prospective	10 control -27 PHT	<17 years	Dynamic compliance (C_{dyn}) = ($D_s - D_d$)/($D_d \times P_S$) × 10^4	• Lower C_{dyn} values in PHT than normal subjects with $P < 0.01$. • Lower RPA wall velocities mean value of PHT vs. control ($P < 0.001$).
Friedberg et al.[15]	Retrospective	31 patients	0–18 years	Pulmonary artery capacitance (PAC) = (PAD × π × VTI)/(PSP − PDP)	• Echo-derived PAC was correlated with cath-derived one ($r = 0.74$, $P < 0.0001$)
Subhedar and Shaw[16]	Prospective	98 (total) 54 with BPD 44 healthy preterm infants	28 days old and >36 weeks	AT/RVETc	• AT/RVET mean for BPD patients lower than control ($P < 0.01$). • AT/RVET was negative correlated with duration of supplemental oxygen treatment in infants with chronic lung disease ($P < 0.0001$).
Evans and Archer[17]	Prospective	38 HMD and 19 control	0–80 hours	TPV:RVET	• Mean TPV/RVET was lower in HMD vs. control subjects by 73–96 hours of life ($P < 0.01$)
Cevik et al.[19]	Prospective	69	• Cases mean 66.9 months. • Control mean 76.3 months.	Ac/RVET AcT InTc DI DecTc TRV AcT/TRV	• There were significant differences between cases and control in all parameters: AcT/RVET, AcT, InTc, DecTc, DI, TRV, and AcT/TRV, except for the RVET. • The InTc and DI parameters were higher in the responder group than in the nonresponder. • Based on the cutoff criterion of 124 msec for AcT, sensitivity was found to be 79.3% and specificity to be 77.5% in distinguishing

(continued)

Table I Continued

Reference	Study Type	Number of Subjects	Age	Echo Parameters	Significant Outcome
					between the PAH patients and healthy control patients. • The sensitivity and specificity for the concomitant use of AcT and/or TRV were found to be 90% and 73%, respectively.
Cooper et al.[20]	Prospective	11 patients with PVR >4.6 U/m^2 10 patients with PVR <4.5 U/m^2	4 months up to 18 years	AcT RVET AcT/RVET PV	• Responder pulmonary hypertension patients showed increase in mean pulmonary artery peak velocity vs. nonresponders, $P < 0.001$). • AcT and AcT/RVET was neither differed significantly between children with high and low pulmonary vascular resistance.
Fitzgerald et al.[21]	Prospective	21 controls and 76 BPD	12–144 months	TPV: RVET	• TPV/RVET mean for BPD subgroups was lower vs. control ($P < 0.005$). • It was suggested that normal ratio is >0.35, possible low ratio was >0.31 up to <0.35 and definitely low <0.31 in patients with definite PHT. • Definite low ratio was detected in 24% of BPD patients and 0% in control.
Fouron et al.[22]	Prospective	10 patients	<20 days	RPET/RET	• Severe BPD was associated with higher RPET/RET (>0.3) with $P < 0.01$ with more mortality than other BPD patients.
Nakahata et al.[23]	Prospective	25 high PVR, 20 low PVR and 23 control	Mean age 1.5 years for 3 groups	AcT InTc DI PV (all done in RA and 100% 0_2)	• InTc (left PA) distinguished patients with high and low PVR (4.7 ± 1.4 vs. 9.9 ± 2.4 with $P < 0.001$) and no significant differences in InTc were found between the low PVR and the control groups. • DI was higher in high PVR vs. low PVR ($P < 0.001$). AcT was lower in high PVR vs. low PVR ($P < 0.001$). • Peak flow velocity was lower in high PVR vs. low PVR with $P < 0.001$. • InTc can differentiate responder vs. nonresponder with cutoff value 6 with sensitivity, specificity, and agreement of 93%, 100%, and 95%, respectively.

(continued)

Table I Continued

Reference	Study Type	Number of Subjects	Age	Echo Parameters	Significant Outcome
Shandas et al.[24]	Prospective	11 patients	3 months up to 18 years	Vel_{prop}	• Vel_{prop} correlates better to PVR (R = 0.87) than to pressure (R = 0.73).
Yates et al.[26]	Prospective	6 controls, 7 moderate BPD, and 8 sever BPD	<1 year old	LV IRT LV MPI RV IRT RV MPI RV E/E′	• RV E/E′ mean for control was lower vs. 6.2 ± 1.4 for moderate BPD (P = 0.03) vs. 7.1 ± 1.9 for severe BPD (P = 0.004). • There is a correlation between BPD category and right ventricle E/E (P = 0.007, R^2 = 0.33) and left ventricular myocardial performance index (P = 0.02, R^2 = 0.28).
Patel et al.[27]	Prospective	28 controls and 15 PHT	<46 days old	RV-E, RV-E′ RV-S, RV-S′ RV-A RV-IVV Septal IVV Septal E′ Septal S′	• RV-E, RV-S, and RV-IVV were significantly lower in PHT vs. control (P < 0.0001, 0.007, and 0.0001, respectively). • Septal E′ and RVE′ were significantly lower in PHT patients than control with P < 0.0001 (E′ was detected only in 46.6% of PHT patients).
Akcan et al.[28]	Retrospective	28 BPD vs. 28 control	7–12 months	TVE TVE/E′ (med) TVE/E′ (lat) TV/E′ (RV) IVRT	• TVE mean was higher in severe BPD vs. mild (P = 0.036). • TVE/E′ (lat) mean was higher in severe BPD vs. mild (P = 0.006). • TVE/E′ (med) mean was lower in control vs. BPD (P = 0.02). • IVRT mean was lower in control vs. BPD (P = 0.001).
Patel et al.[30]	Prospective	28 controls and 16 PHT	<1 month	RV_{MPI}	• PHT group showed a higher RVMPI (0.55 ± 0.17) than the control group (0.24 ± 0.09) (P < 0.0001).
King et al.[31]	Prospective	20 controls, 12 mild/moderate PHT and 17 sever PHT	2 weeks–20 years	Normalized septal radius of curvature	• The mean end-diastolic septal curvature for patients with RV systolic pressure <50% systemic was flatter than that for normal with P < 0.02). • Patients with right ventricular systolic pressures that were greater than 50% of their systemic pressures demonstrated end-diastolic septal flattening that progressed throughout systole.

(continued)

Table I Continued

Reference	Study Type	Number of Subjects	Age	Echo Parameters	Significant Outcome
					• A statistically significant difference ($P < 0.0001$) was found between the mean septal radii of curvature for both groups of PHT (<50% and > 50% of systemic pressure) during mid systole and end systole.
Del Cerro et al.[33]	Retrospective	29 BPD with PHT median 70% of systemic pressure	Median age 4.5 months at diagnosis	TRJ IVS morphologies	• PH was considered moderate in 52% and severe in 48% of patients. Basal IVS morphology was mostly type II but during follow-up, the most common morphology was type I.

PHT = pulmonary hypertension; AcT/RVET = acceleration time/right ventricular ejection time; AT = acceleration time; TSm, tricuspid systolic motion; SD/DD = systolic to diastolic time ratio; VTI = velocity tissue integral; PAC, pulmonary artery capacitance; InT = inflection time; DI = deceleration index; TRV = tissue velocity integral; RVET = right ventricle ejection time; IVS = interventricular septal; TR = tricuspid regurgitation; IVV = isovolemic velocity; IVRT = isovolemic relaxation time; DecTc = corrected deceleration time; PV = pulmonary artery peak velocity.

Doppler envelope, TR peak velocity can be used to predict PAP using the modified Bernoulli equation ($4 \times [\text{velocity of TR}]^2$) to convert this velocity to a pressure gradient with cutoff value more than 3 m/sec. This has a good correlation (up to 0.95) to invasive cardiac catheterization-based measurement.

In the absence of reliable well-enveloped TR jet and presence of Pptent ductus arteriosus (PDA), left pulmonary artery (LPA) flow analysis can be used rather than main pulmonary artery (MPA) or right pulmonary artery (RPA). The parameters included in LPA flow analysis (with their respective cutoff values) are InTc (<4.3 msec), AT/RVET (<0.31), and deceleration index (>0.4).[23] In addition, EI and TAPSE can also be used, but TDI values cannot be used due to presence of PDA.[34]

In absence of TR jet and right to left PDA shunt, either the eccentricity index (<0.81) or TAPSE (<0.5 cm) can be used, because LPA flow analysis is unreliable in PDA with right to left shunt.[23] Presence of right to left shunt through PDA means mean pulmonary artery pressure (MPAP) is at least above mean systemic pressure. Also strain and strain rate could possibly be used in this category but strain/strain rate are still under investigation for adult PHT.[35,36] No pediatric studies using strain measurement for PHT have been published so far.[37–39] In the absence of reliable TRJ with absence of PDA, any of the following parameters can be used including: tissue Doppler of right ventricle (with cutoff values of RV-IVV<5.2 cm/sec, RVS (TSM) <7.6 cm/sec, and RV-E′ < -4.3 cm/sec); LPA flow analysis; TAPSE; or eccentricity index.

Discussion:

The development of this echocardiography protocol is meant to aid clinicians in the screening of infants who are at high risk for the development of PHT. This is not meant to replace the use of cardiac catheterization data, which still remains the gold standard for the diagnosis of PHT in infants with BPD. Because echocardiography is noninvasive, portable, and widely available, the development of a standardized screening approach can be helpful in the different clinical situations that are encountered in infants with BPD. Even though there are many echocardiographic parameters that have been reported in the adult literature, these cannot be directly extrapolated to pediatric age groups due to differences in the anatomy and physiology.

Reliable TRJV showed high sensitivity and specificity to detect PHT in multiple studies as discussed before. Unfortunately, PHT can occur without TR jet or with TR but unreliable Doppler envelope. Studies showed that a reliable TRJ

TABLE II

Techniques for Non-TR Quantitative Assessment on Echocardiography

Parameters	Technique	Figure	Echocardiographic Window
Acceleration time/right ventricular ejection time (AcT/RVET)	Ratio between acceleration time and ejection time	2B	Parasternal short-axis (base) Doppler
Deceleration index (DI)	Ratio between results of subtraction of inflection flow from peak flow to peak flow	3A	Parasternal short-axis (base) Doppler
Velocity propagation (VP)	Ratio between result of subtraction of two distances to result of subtraction of 2 times	3B	Parasternal short-axis (base) colored M-mode
Tricuspid annular plane systolic excursion (TAPSE)	TAPSE in mm (ASE)	2D	Apical four-chamber M-mode
Tissue Doppler image (TDI)	TDI (RV-IVV, RV-S, RV-E′, and MPI) (ASE)*	2A	Apical four-chamber TDI
Eccentricity index (EI)	Ratio of the length of two perpendicular minor-axis diameters, one of which bisected and was perpendicular to the ventricular septum (ASE)*	2C	Parasternal short-axis (papillary muscle level)

TDI = tissue Doppler image; TR = tricuspid regurgitant; IVV = isovolemic velocity.
*From the American Society of Echocardiography (ASE) Guidelines for the Echocardiographic Assessment of the Right Heart in Adults.[44]

may not be seen in up to 85% of patients with BPD associated PHT, and qualitative studies generally have low sensitivity and specificity in this situation. Hence, there is a need for a standardized approach toward the echocardiographic assessment of pediatric PHT and it cannot solely depend on tricuspid regurgitation or quantitative parameters of right heart side.

Since it was first described by Fuoron et al.[22] 36 years ago, cardiologists have tried to find the most reliable noninvasive echocardiographic parameter that represent pulmonary pressure accurately. Czernik et al.[40] found echocardiographic findings can be significant by 14 days of age in detecting PHT in BPD infants versus non-BPD infants. Murase and Ishida[18] found that gestational age is one of the main determinants for PHT in very low birthweight (VLBW) infants. PHT was present in the first 48 hours in VLBW with gestational age more than 30 weeks detected by echocardiography versus who were less than 30 weeks may not have shown PHT until 14 days of life.

To the best of our knowledge, ours is the only systemic review of the literature regarding different echocardiographic parameters to evaluate PHT in patients with BPD. On the basis of this review of all the pediatric studies listed in Table II, we have proposed an echocardiographic algorithm that can help to identify PHT using other echocardiographic parameters for specific situations such as lack of TR jet, or in the presence of PDA.

There are limitations to the use of this echocardiography screening approach. The use of this protocol implies a good knowledge of some of the less commonly used echocardiographic indices and this may require special training for assessment of some of these parameters. There is significant operator variability in pediatric echocardiography, and some of the infants with BPD can be very challenging in terms of getting a reliable echocardiogram done. Cardiac catheterization still remains the gold standard for the diagnosis of PHT in the BPD population, but in many cases it may not be feasible because of poor pulmonary reserve in these patients. Some studies did not report concomitant cardiac catheterization data for the study subjects to validate their echocardiographic parameters. In addition, a few echocardiography parameters that we have discussed were initially evaluated in adult populations or have been used for the assessment of PHT in non-BPD populations. Hence, the adoption of a more uniform screening and diagnostic approach may help to generate more long-term data regarding these echocardiographic parameters in BPD infants with PHT.

There is increasing recognition of other noninvasive markers of pediatric PHT that are being considered. Colvin et al.[41] recently summarized the existing literature on the use of biomarkers for pediatric PHT. These could be developed for use either alone or in combination with echocardiography data and future studies may help define a combined approach for pediatric patients. Even though cardiac MRI is nowadays considered a better tool for assessment of the right ventricle than echocardiography, the need

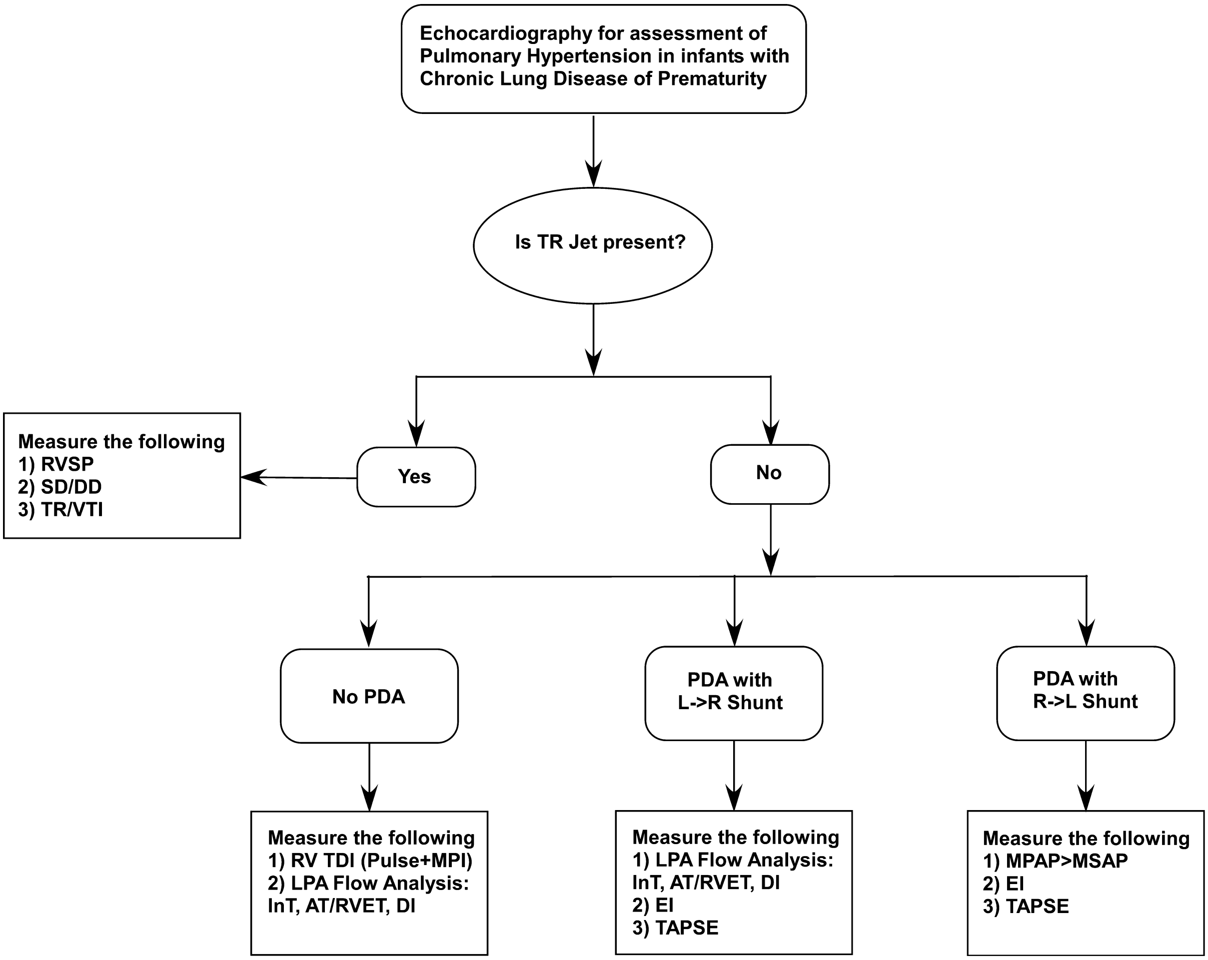

Figure 4. Screening algorithm for assessment of pulmonary hypertension in infants with BPD. TR = tricuspid regurgitation; RVSP = right ventricular systolic pressure; SD/DD = systolic to diastolic time ratio; VTI = velocity tissue integral; InT = inflection time; AT = acceleration time; RVET = right ventricle ejection time; DI = deceleration index; EI = eccentricity index; MPAP = mean pulmonary artery pressure; MSAP = mean systemic artery pressure; TAPSE = tricuspid annular plane systolic excursion.

for sedation for the former in pediatric patients makes it a limiting factor for its widespread use.

Our algorithm detects PHT in different anatomical/physiological situations. For PHT with right to left shunt across a PDA, there is insufficient evidence to support the use of one echocardiographic modality over the others. But the presence of right to left shunt is in itself an indication that pulmonary pressures are probably higher than systemic pressures.[42] Finally, strain and strain rate are considered a "black box" in pediatric PHT. Although it has been studied extensively in adult literature,[35,43] most of the pediatric literature is still establishing norms for neonates and assessing the effect of PDA on strain and strain rate.[38,39]

Conclusions:

Pediatric PHT has its own unique characteristics and its assessment cannot be just extrapolated from the data from adult studies. On the basis of systematic review of the existing literature, we have proposed a new echocardiography-based screening strategy for assessment of PHT in infants with chronic lung disease of prematurity. Further studies will be necessary to confirm its validity.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Details of the search methodology for the systematic review.