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Pediatric and Congenital Heart Disease (G Singh, Section Editor)

Evaluation and Monitoring of Pulmonary Hypertension in Neonates With Congenital Diaphragmatic Hernia

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Abstract

Purpose of review This review aims to describe the assessment of pulmonary hypertension and ventricular function in neonates with congenital diaphragmatic hernia and the long-term follow-up of their pulmonary vascular disease.
Recent findings In 2015, the pediatric pulmonary hypertension guidelines from the American Heart Association and American Thoracic Society suggested class I level of evidence B guidelines for routine evaluation of patients with congenital diaphragmatic hernia, including longitudinal care in an interdisciplinary pulmonary hypertension program and following the recommendations offered for all children with pulmonary hypertension.
Summary Congenital diaphragmatic hernia causes compression of the lungs during critical stages of fetal development and results in lung hypoplasia. As a result, there is abnormal development of pulmonary vasculature that leads to post-natal pulmonary hypertension and increased afterload to the right ventricle. Left ventricular filling is affected by decreased pre-load and mechanical compression by abdominal content leading to decreased systemic perfusion. Persistent pulmonary hypertension after surgical repair of congenital diaphragmatic hernia is associated with increased mortality. Assessment and monitoring of pulmonary hypertension and ventricular function in this population of neonates is crucial to determine response to medical treatment, the need for extracorporeal membrane oxygenation, and the timing of surgical repair.

Introduction

Congenital diaphragmatic hernia (CDH) is a complex congenital anomaly, whereby a defect in the diaphragm allows for the herniation of abdominal viscera into the thoracic cavity. The abdominal viscera in the chest compresses the lungs during critical stages of fetal development and cause pulmonary hypoplasia. Defects can occur posterolaterally (Bochdalek hernia) in approximately 70%, anteromedially (Morgagni hernia) in about 25%, and centrally in 5% of patients [1–4]. Bochdalek hernias tend to be associated with the most severe phenotype leading to pulmonary hypoplasia [5].

International population-based studies cite the incidence of CDH as approximately 1:2000 to 1:5000 live births with a slight predisposition of the male sex [6–10]. Environmental factors may play a role in CDH; however, a variety of genetic variations are implicated in about 30% of cases [11••]. CDH may be isolated or associated with many additional anomalies. Congenital heart defects occur in about 10–35% of patients [12].

Normally, lung angiogenesis and alveologenesis occur interdependently in utero. CDH can lead to lung hypoplasia and abnormal development of the pulmonary vasculature and parenchyma leading to varying degrees of hypoxemic respiratory failure, pulmonary hypertension (PH), and cardiac dysfunction [13••]. After birth, the pulmonary vascular resistance (PVR) remains high due to abnormally developed pulmonary vasculature. Left untreated, pulmonary arterial muscularization and neointimal proliferation can follow, significantly reducing the total pulmonary vascular bed cross-sectional area. Pulmonary vascular reactivity and the process of vascular remodeling are unpredictable, and PH ensues. CDH-related PH is considered secondary and is classified within World Health Organization NICE classification group 3 (*PH due to lung disease*) and Panama classification category 2 (*perinatal pulmonary vascular maladaptation*) [13••, 14].

The severity of PH is not the only hemodynamic factor that determines outcomes in neonates with CDH. Decreased ventricular systolic function has been associated with the need for extracorporeal membrane oxygenation (ECMO) support and may explain the lack of improvement with pulmonary vasodilators in more severe CDH cases [15••, 16]. In the setting of PH, the right ventricle (RV) augments its contractility in response to increased afterload to maintain adequate pulmonary blood flow (RV-pulmonary artery coupling) [17]. Failure of adaptation of the RV to elevated PVR leads to decreased left ventricle (LV) preload, resulting in hypoxemia and hypotension [15••]. The LV preload in neonates with CDH is also affected by the abnormal ventricular septum configuration and external compression by abdominal contents in the chest [18]. Decreased LV filling leads to left atrial hypertension and secondary pulmonary venous hypertension, limiting the effect of pulmonary vasodilators. Severely diminished LV systolic function may lead to RV-dependent systemic circulation via right-to-left shunting at the ductus arteriosus [4]. Hypoxemia ensues from right to left shunting not only at the arterial level but also through the patent foramen ovale and from hypoxemic respiratory failure. Ultimately, the pressure overload on the RV as the ductus arteriosus closes, coupled with a fall in cardiac output and resultant ischemia, leads to right heart failure and death.

The natural history of CDH is death within the first few days to years of life, usually from respiratory failure and PH. The survival of CDH has improved over the past 20 years. A recent international prospective cohort study found the in-hospital mortality to be around 29% [19]. Reported 1-year survival rates are between roughly 20 and 45% [6, 20]. Long-term studies elucidating mortality beyond the first year of life are sparse but suggest additional attrition beyond 1 year [20]. This review aims to describe the assessment of PH and ventricular function in neonates with CDH and the recommendations for long-term follow-up of pulmonary vascular disease in this population.

Cardiac catheterization assessment of neonates with congenital diaphragmatic

Pulmonary artery pressure and cardiac output measurements are best obtained via right cardiac catheterization with acute vasoreactivity testing (AVT). Strictly

speaking, PH is defined by cardiac catheterization as a mean pulmonary artery pressure (MPAP) greater than 25 mmHg [21••]. AVT is performed using a combination of inhaled nitric oxide 20–80 ppm, 100% oxygen, inhaled or intravenous prostaglandin I_2 analogs, or sildenafil. A positive AVT response, defined as at least a 20% reduction in MPAP with increase in cardiac output; and a reduction or no change in PVR/SVR ratio, was proposed by Barst [22] to determine the likelihood of reversibility in PH to calcium channel block therapy in pediatric idiopathic pulmonary arterial hypertension patients. The applicability of this criterion to CDH patients is controversial; however, there is no other alternative for assessing pulmonary vasodilator response in this patient group.

Catheterization is invasive and carries a significant risk of morbidity and mortality in CDH patients given small size, need for general anesthesia, radiation exposure, and risk of cardiopulmonary collapse. When performed early in the course of CDH, findings are inherently almost always consistent with PH given the natural history of the disease and transitional pulmonary vascular physiology, despite the use of pulmonary vasodilators early in the postnatal period. For those reasons, some investigators recommend against routine cardiac catheterization in the assessment of PH in CDH patients [13••, 23••] and prefer monitoring with echocardiography.

This manuscript's authors advocate for cardiac catheterization with AVT to determine the efficacy of maintenance or titration of pulmonary vasodilator therapy after CDH repair, as recommended by Abman et al. [21••], and for prognosis assessment.

Echocardiographic evaluation of neonates with congenital diaphragmatic

Assessment of pulmonary hypertension severity

Echocardiographic measurements of systolic, mean, and end-diastolic pulmonary artery pressures are used to detect and monitor PH in clinical practice. However, these measurements are often inaccurate or unobtainable in young children [24]. Regardless of the limitations of echocardiography, several studies have used echocardiographic parameters to demonstrate the association of PH severity with clinical outcomes in CDH, including tricuspid regurgitation (TR) jet peak velocity, patent ductus arteriosus flow direction and velocity, ventricular septum configuration in end-systole, and pulmonary artery acceleration time.

Tricuspid regurgitation jet peak velocity

The peak velocity of the TR jet is used to estimate systolic pulmonary artery pressure (SPAP). The TR jet peak velocity is obtained using continuous wave Doppler across the tricuspid valve annulus. This velocity is entered into the modified Bernoulli equation to calculate the systolic pressure gradient across the tricuspid valve. The RV systolic pressure (RVSP) is then calculated by adding the systolic right atrial pressure (RAP) to this pressure gradient. In the absence of RV outflow tract obstruction, RVSP is equal to SPAP.

$$\text{SPAP} = \text{RVSP} = 4 \times \left[(\text{TR jet peak velocity})^2\right] + \text{RAP} \quad (1)$$

In clinical practice, there is no reliable, non-invasive method for estimating RAP in infants [25]. As a result, RAP is generally ignored in Eq. (1) [24, 26••]. Despite this limitation, the TR jet-based estimate of RVSP has an excellent correlation with simultaneous invasive measurements of RVSP in both children and adults ($r = 0.96$) [27].

Previous studies of outcomes in CDH have used echocardiography to grade severity of PH by comparing SPAP to the systolic arterial pressure (SAP) as follows: no/mild PH is SPAP < 2/3 times SAP, moderate PH is SPAP ≥ 3/4 times SAP and SPAP < 1 time SAP, and severe PH is SPAP ≥ 1 time SAP [26••, 28].

The TR jet method of estimating SPAP relies on the quality of the TR jet signal [29] (Fig. 1). In a longitudinal study of infants with CDH, only 38% of echocardiograms had adequate TR jet signals that allowed estimation of RVSP [26••]. The authors also reported that patients with severe PH are more likely to have an adequate TR jet signal than patients with no/mild PH (81% versus 19%, $p < 0.01$). However, the accuracy of the TR jet method in estimating right heart catheterization-derived RVSP, defined as 95% limits of agreement ± 10 mmHg, is lower in the setting of higher RVSP (76% in children with RVSP ≥ 1/2 time SAP and 67% in children with RVSP ≥ 2/3 times SAP) [30].

Patent ductus arteriosus flow direction and velocity

The direction of flow across the patent ductus arteriosus (PDA) is an indicator of the pressure gradient between the aorta and the main pulmonary artery (Fig. 2). The presence of right-to-left shunting throughout the cardiac cycle indicates supra-systemic SPAP, while the presence of bidirectional shunting across the PDA indicates near-systemic SPAP [31]. Continuous left-to-right shunting

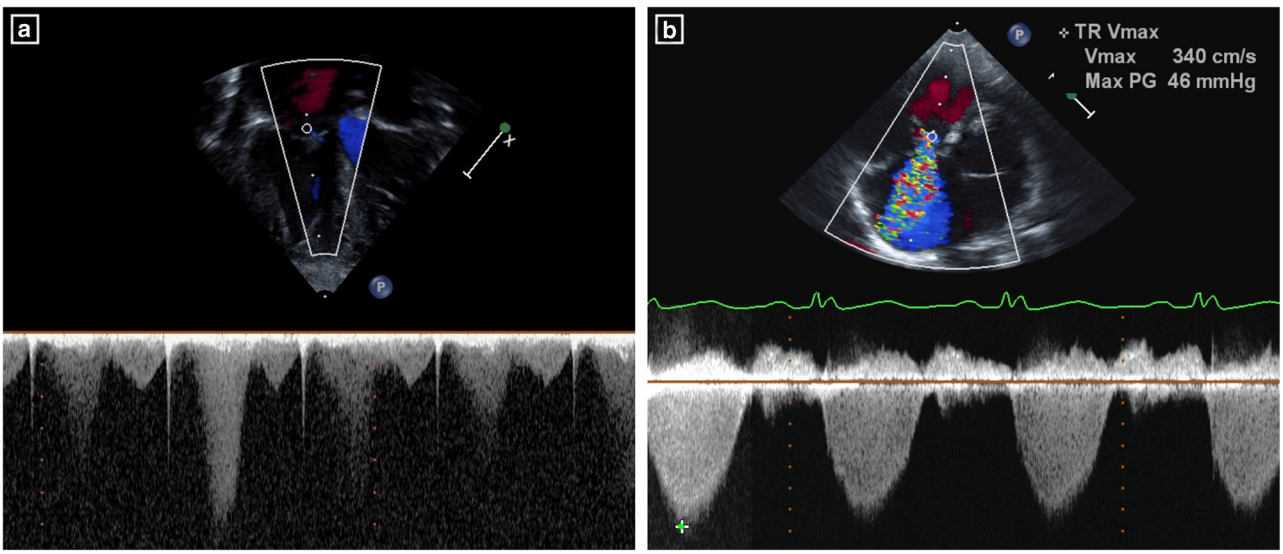

Fig. 1. **a** Inadequate TR jet Doppler signal for estimation of RVSP. **b** Adequate TR jet Doppler signal estimates RVSP as 46 mmHg plus RAP.

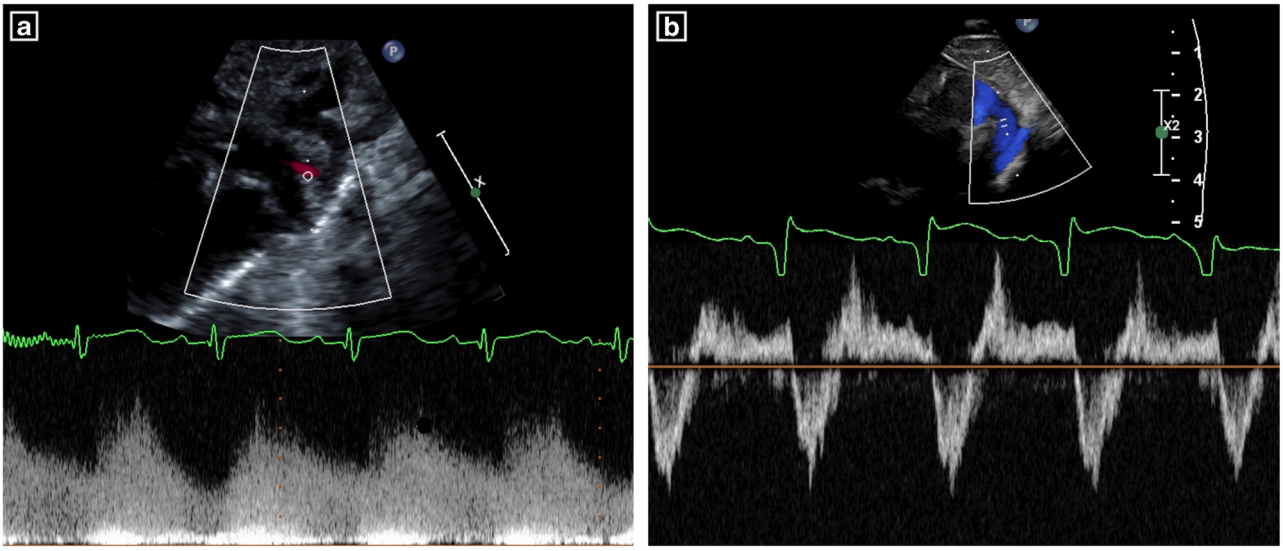

Fig. 2. **a** Spectral Doppler signal across PDA with continuous left to right shunting indicates subsystemic systolic pulmonary artery pressure. **b** Bidirectional shunting across PDA indicates systemic or near systemic SPAP.

across the PDA indicates subsystemic SPAP and allows for quantitative measurement of SPAP [31]. The peak aorta-to-pulmonary artery systolic gradient is calculated from the PDA peak systolic velocity using the modified Bernoulli equation. This pressure gradient is subtracted from the SAP to obtain the SPAP

$$\mathrm{SPAP} = \mathrm{SAP}{-}4 \times \left[(\text{PDA peak systolic velocity})^2\right] \quad (2)$$

Estimation of SPAP based on PDA flow direction is more accurate than the TR jet method [26••]. However, the prevalence of PDA in neonates with CDH drops significantly in the first few weeks of life. A PDA is found in 85% of echocardiograms performed within the first 48 h of life in term neonates with CDH, but only 43% and 19% of scans at 1 week and 4 weeks of life, respectively [26••].

Ventricular septum configuration in end-systole

In the absence of adequate TR jet or PDA, assessment of the ventricular septum configuration is commonly used to estimate PH severity in neonates with CDH. End-systolic flattening of the ventricular septum correlates with more than half-systemic RVSP, while end-systolic bowing of the ventricular septum towards the LV correlates with supra-systemic RVSP [32]. This qualitative method is easily obtained from parasternal or subcostal short-axis views. The degree of leftward shifting of the ventricular septum can be quantified with the systolic LV eccentricity index (LVEI), which is calculated as the ratio of the largest LV diameter parallel to the septum to the LV diameter perpendicular to the ventricular septum in end-systole [33] (Fig. 3). LVEI has a significant positive correlation with invasive measurements of RV-to-aortic systolic pressure ratio in children

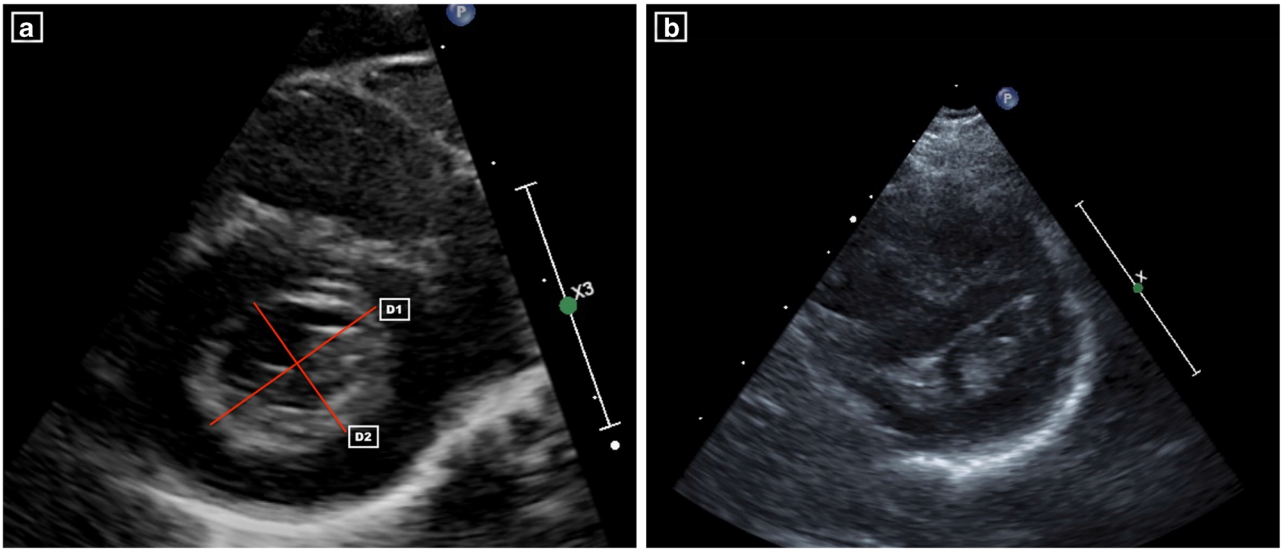

Fig. 3. a Parastenal short-axis view of the LV at the level of the papillary muscles in end-systole. Round configuration of the ventricular septum indicates less than half-systemic RVSP. D1, largest LV diameter parallel to the ventricular septum. D2, LV diameter perpendicular to the ventricular septum. LVEI = D1/D2. **b** Flattening of the ventricular septum in end-systole indicates more than half-systemic RVSP.

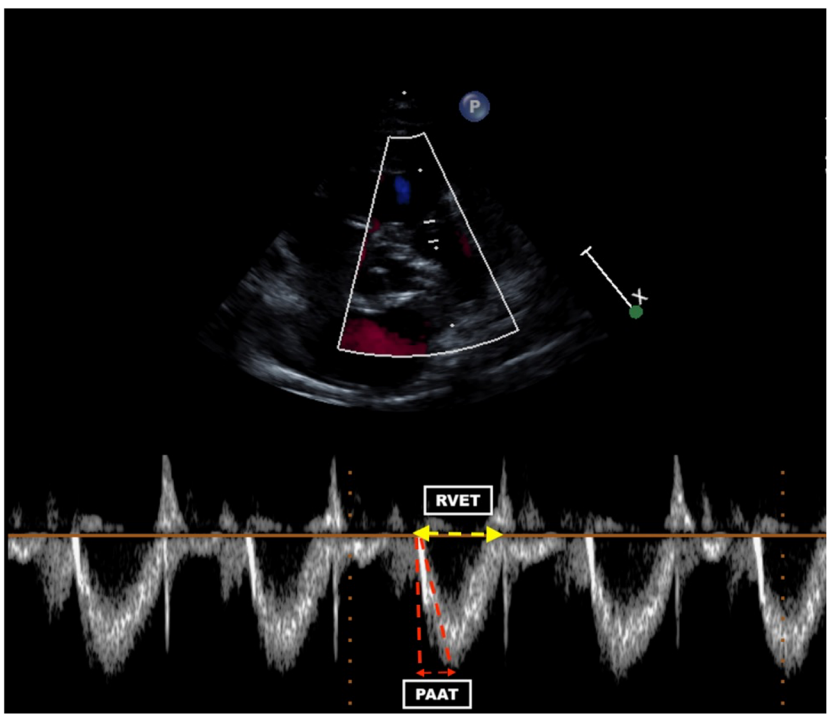

Fig. 4. Pulsed-wave spectral Doppler signal at the level of the pulmonary annulus. PAAT is the time interval between the onset of systolic pulmonary arterial flow and peak pulmonary arterial flow velocity. RVET is the time interval between the onset of RV ejection and cessation of antegrade pulmonary blood flow.

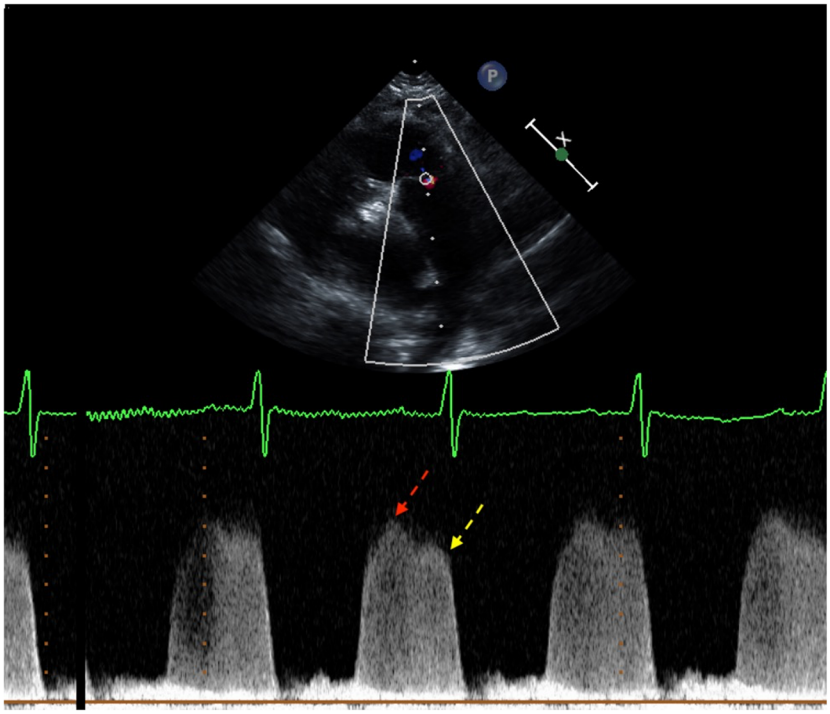

Fig. 5. Pulmonary artery regurgitation Doppler signal. The red arrow indicates the early peak diastolic pulmonary artery regurgitation velocity used to calculate MPAP. The yellow arrow indicates the end-diastolic pulmonary artery regurgitation velocity used to calculate the EDPAP.

($r = 0.76$, $p < 0.001$). LVEI > 1.48 has a sensitivity of 76% and a specificity of 100% in predicting more than half-systemic RVSP [34].

Pulmonary artery acceleration time

Pulmonary artery acceleration time (PAAT) is the time interval between the onset of systolic pulmonary arterial flow and peak pulmonary arterial flow velocity measured by pulsed-wave spectral Doppler at the level of the pulmonary valve (Fig. 4) [35]. PAAT is an indicator of the interplay between PVR, pulmonary vascular compliance, and RV systolic function [36, 37]. PAAT has an inverse correlation with SPAP measured by cardiac catheterization and can be used to calculate SPAP in children [35]. The accuracy of this calculation can be affected by flow turbulence in the RV outflow tract, which can alter the contour of the spectral Doppler envelope, preventing clear identification of the point of peak pulmonary arterial flow velocity [38]. Despite this limitation, PAAT can be calculated for 99% of pediatric echocardiograms [39]. In addition, normal reference values and *z*-score calculations based on body surface area, length, and weight have been published for PAAT in the pediatric population [39].

One caveat to using PAAT to detect PH is the inverse correlation of PAAT with heart rate. The normal reference values for PAAT in children are determined for specific ranges of heart rates, which limits the utility of PAAT when the heart rate is greater than 2 standard deviations above normal for age [39]. To account for the effect of heart rate, PAAT can be divided by RV ejection time

(RVET). In children, a PAAT/RVET less than 0.31 has a sensitivity of 87%, a specificity of 89%, and an area under the curve of 0.92 (95% CI, 0.84–0.99) for detection of PH, as defined by MPAP greater than 25 mmHg [35]. A value of PAAT/RVET to detect PH in neonates has not been determined. However, the work of Kipfmueller et al. [40•] suggests potential clinical utility for PAAT/RVET in the monitoring of neonates with CDH. They found that PAAT/RVET less than 0.29 within the first 6 h of life predicts need for ECMO or early mortality in this population with a sensitivity of 87%, a specificity of 68%, a positive predictive value of 62%, and a negative predictive value of 90%.

Pulmonary regurgitation

In contrast to the previously described echocardiographic parameters which estimate SPAP, continuous wave Doppler interrogation of the pulmonary regurgitation jet allows estimation of MPAP and end-diastolic pulmonary artery pressure (EDPAP) (Fig. 5). Pulmonary regurgitation has not been specifically evaluated in the setting of CDH, but it is a useful method to detect PH in children and adults in the absence of an adequate TR jet [41]. The formulas to calculate MPAP and EDPAP are as follows:

$$\mathrm{MPAP} = 4 \times \left[(\text{early peak pulmonary regurgitation velocity})^2\right] + \mathrm{RAP} \quad (3)$$

$$\mathrm{EDPAP} = 4 \times \left[(\text{end–diastolic pulmonary regurgitation velocity})^2\right] + \mathrm{RAP} \quad (4)$$

Additional echocardiographic indicators of pulmonary vascular disease in congenital diaphragmatic hernia

In addition to monitoring PH, echocardiography allows assessment of structural factors related to pulmonary vascular disease in neonates with CDH.

Size of branch pulmonary arteries

Branch pulmonary artery diameter correlates with the severity of lung hypoplasia and post-natal outcomes in CDH [42]. Okazaki et al. [43] studied term neonates with left-sided CDH and found that the left pulmonary artery (LPA) diameter at birth is significantly smaller in non-survivors than in survivors [43]. Additionally, the ratio of the LPA to the right pulmonary artery (RPA) is significantly lower in neonates that require treatment with nitric oxide compared to those that do not need nitric oxide.

Pulmonary venous drainage

Neonates with CDH usually have unobstructed pulmonary venous return to the left atrium at birth. However, late-onset pulmonary vein stenosis (PVS) after CDH repair has been reported as a cause of rapidly progressive and fatal PH, despite a period of normal of SPAP [4, 44]. Serial evaluation of the pulmonary veins with spectral Doppler should be performed to detect increased pressure

gradients in the pulmonary veins of patients with CDH. If there is a concern for PVS, cardiac catheterization should be considered for detailed evaluation of the pulmonary veins and potential therapeutic intervention.

Assessment of right ventricle size

RV size in neonates with CDH is an important indicator of the response of the RV to high PVR. The complex morphology of the RV and the presence of lung and bone artifacts make echocardiographic assessment of the RV difficult [45]. The pediatric echocardiography guidelines recommend assessing RV size by obtaining minor axis diameters, major axis length, and end-diastolic area from the apical four-chamber view. However, these measurements underestimate RV size [46]. Moreover, normal values for RV size in children are not available [45]. Assessment of RV size with volumetric calculations using two-dimensional echocardiography relies on imprecise geometric assumptions and is discouraged by the current pediatric guidelines [46].

Assessment of left ventricle size

In fetal life, there is often mild-to-moderate left heart hypoplasia secondary to compression of the cardiac mass by abdominal organs, decreased preload due to lung hypoplasia, and abnormal blood return from the inferior vena cava to the heart [47]. Following CDH repair, LV size tends to normalize.

LV size in children is commonly measured using short-axis LV diameters in end-systole and end-diastole. These parameters accurately reflect LV size only when the LV short-axis geometry is circular, which is often not the case in infants with CDH and severe PH [46]. Estimation of LV volume using two-dimensional echocardiography can be used as an alternative assessment of LV size. Calculation of LV volume requires the acquisition of multiple views with a clear definition of the blood-endocardium border and long-axis measurements of the LV that are not foreshortened [46]. Obtaining appropriate views for these measurements in neonates with CDH is difficult due to the presence of lung artifact and the abnormal position of the heart in the chest.

Due to the limitations on echocardiographic assessment of ventricle size in neonates with CDH, cardiologists most often rely on visual comparison of serial studies to assess for changes over time.

Assessment of ventricular function

As with assessment of ventricular size, echocardiographic evaluation of ventricular function in neonates with CDH is challenging. Standard measurements of RV systolic function include fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). Standard echocardiographic measurements of LV systolic function include shortening fraction (SF) and ejection fraction (EF). In addition, myocardial performance index (MPI) and myocardial strain are new parameters of ventricular function that have been associated with clinical outcomes in neonates with CDH.

Fractional area change

The percentage change of the RV area from end-diastole (RVAED) and RV area from end-systole (RVAES) is measured by two-dimensional echocardiography from an RV-focused four-chamber view

$$\mathrm{FAC}(\%) = [(\mathrm{RVAED}-\mathrm{RVAES})/\mathrm{RVAED}] \times 100. \quad (5)$$

The normal value of FAC in healthy full-term neonates is 33 ± 5% at birth and increases to 39 ± 4% by 1 month of age [48]. The applicability of FAC to neonates with CDH is limited by a significant lung artifact and an abnormal position of the heart in the chest, which make it difficult to visualize the RV free wall, the blood-endocardium border, and the apex of the heart, all of which are needed to measure RVAED and RVAES [46].

Tricuspid annular plane systolic excursion

The RV contracts primarily in the longitudinal direction, with displacement of the tricuspid annulus towards the apex in systole. TAPSE is a measurement of this displacement. The M-mode line of interrogation is placed along the RV free wall passing through the tricuspid valve annulus to track its motion from the highest position to the lowest descent during ventricular systole (Fig. 6) [49]. Despite being a regional measurement of RV function, TAPSE has a good correlation with RV EF in adults [50]. There are normative data available in the pediatric population. Normal mean TAPSE for term neonates is 0.91 cm (*z*-score ± 3, 0.56–1.26 cm) [51].

Left ventricular shortening fraction

Shortening fraction (SF) is the fractional change of the LV dimension from end-diastole to end-systole in the parasternal short-axis view [30]. SF can be

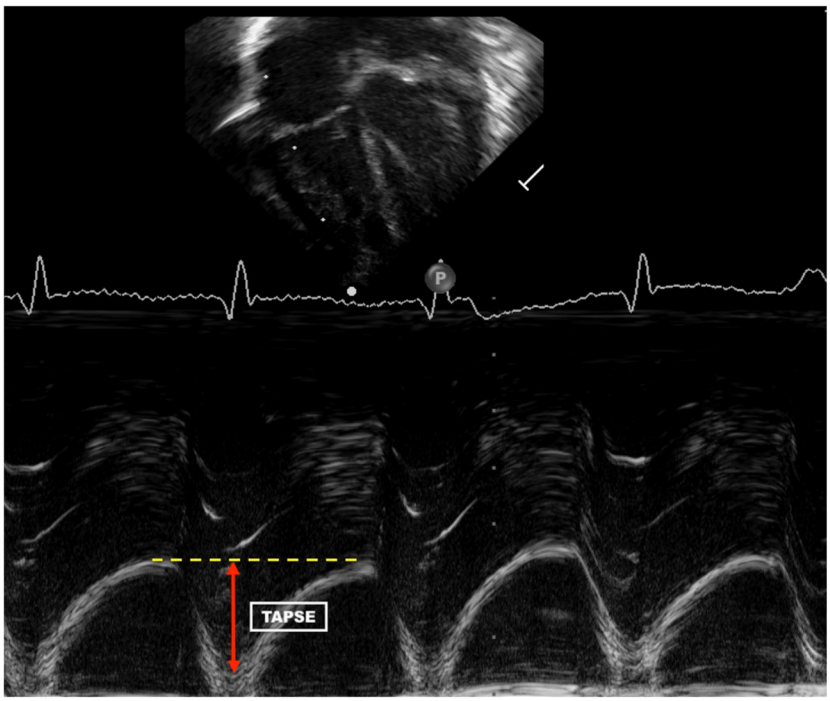

Fig. 6. TAPSE measurement from M-mode tracing of the right ventricular free wall passing through the tricuspid valve annulus.

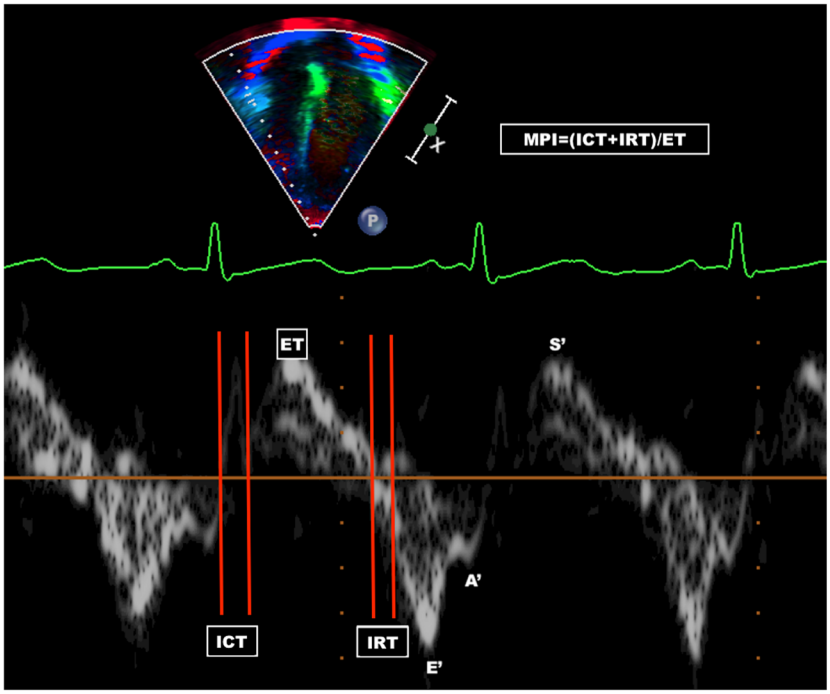

Fig. 7. Tissue Doppler signal obtained from the right ventricular free wall at the level of the tricuspid valve annulus. Vertical red lines separate time intervals for calculation of MPI. ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET, ejection time. *E'*, peak early diastolic velocity; *A'*, peak late diastolic velocity; *S'*, peak systolic velocity.

measured by M-mode or two-dimensional echocardiography. This method is highly reproducible, but it can only be applied in the setting of normal configuration of the ventricular septum.

Left ventricular ejection fraction

EF is the percentage change in volume from end-diastole to end-systole. The methods to calculate EF include the summation discs and area length [30]. Both methods require adequate differentiation of the endocardium border and are affected by loading conditions.

Myocardial performance index

MPI is a dimension-independent measurement of systolic and diastolic function that can be applied to the right and left ventricles [52]. MPI is the ratio derived from the sum of the isovolumic contraction time (ICT) and isovolumic relaxation time (IRT), divided by the ejection time (ET) [53]. The formula $(a - b) / b$ where a equals the sum of ICT plus ET plus IRT, and b equals ET can be used to facilitate the measurements of the time intervals (Fig. 7).

$$\mathrm{MPI} = (\mathrm{ICT} + \mathrm{IRT})/\mathrm{ET} = (a{-}b)/b \tag{6}$$

MPI increases in the presence of ventricular dysfunction due to the lengthening of ICT and IRT and shortening of ET [54]. Measurement of MPI can be done using spectral Doppler and tissue Doppler imaging. Spectral Doppler measurements are based on flow signals while tissue Doppler measurements are based on myocardium velocity signals [52]. Normal MPI values during the neonatal period vary due to changes in ventricular relaxation and compliance, changes in RV pre-load following the closure of the PDA, and drop in the PVR [55]. RV and LV MPI values above 0.5 are abnormal irrespective of the spectral Doppler technique utilized or the age of the infant [56, 57].

In adults with PH, RV MPI is a determinant of clinical outcomes [58]. In neonates with CDH, RV MPI is significantly elevated in the first 48 h of life and decreases after surgical repair of CDH [59].

Speckle-tracking echocardiography-derived longitudinal strain

Strain is defined as the percentage change in the length of a myocardial segment from diastole to systole and is expressed as a negative percentage (Fig. 8). Longitudinal strain is the most vulnerable component of myocardial mechanics and detects early changes in myocardial function before standard echocardiographic parameters of ventricular ejection [61]. The magnitude of strain is affected by changes in ventricular contractility and loading conditions [62]. Two-dimensional speckle-tracking echocardiography is the most frequently used method to measure LV and RV longitudinal strains in children. Normative

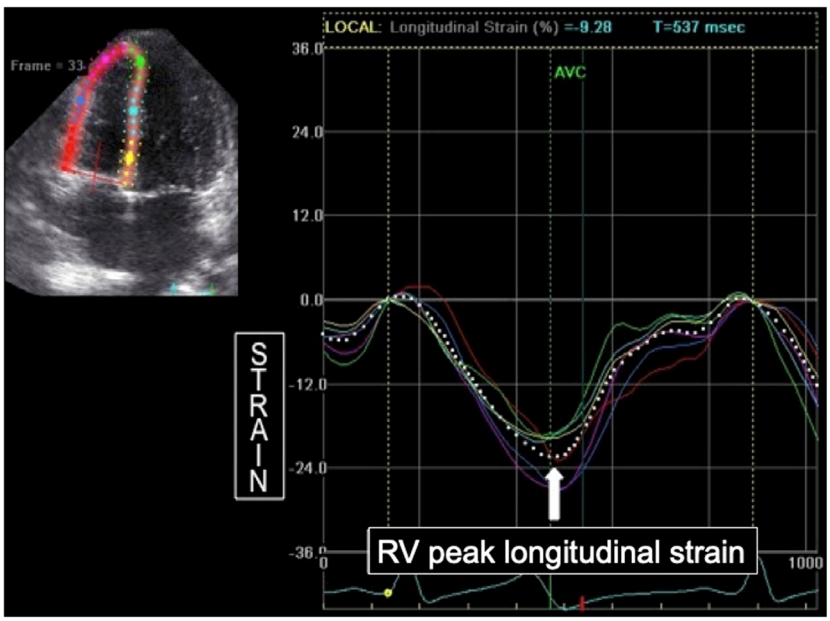

Fig. 8. Modified from Sanchez et al. [60] with permission from John Wiley and Sons (Copyright © 2014, John Wiley and Sons). The image in the left upper corner is an upside-down four-chamber view of the heart demonstrating tracking of myocardial segments of the RV by two-dimensional speckle-tracking echocardiography. The graph on the right shows the variation of strain during the cardiac cycle. The strain values obtained from each segment of the RV are represented by colored curves. The color of each curve corresponds to the color of the segment being tracked in the image on the left. The dotted white line represents the average strain at each point in the cardiac cycle. The most negative point in the dotted white line represents the RV peak longitudinal strain.

data for two-dimensional speckle-tracking-derived LV and RV longitudinal strains is available in the pediatric population [63, 64].

In adults with PH, RV longitudinal strain estimates the myocardial response to pressure overload and predicts the development of right heart failure and death [65, 66]. In neonates with CDH, LV and RV longitudinal strains are significantly depressed within the first few days of life when compared to healthy controls [16]. Moreover, neonates with CDH that require ECMO support have lower LV and RV longitudinal strains than neonates that do not require ECMO[15••].

Assessment of flow direction at the foramen ovale

The normal flow direction across the foramen ovale is from left to right. In the setting of elevated PVR and secondary decreased RV compliance, flow across the foramen ovale is either right to left or bidirectional [67]. In infants with CDH and severe PH, this atrial communication provides decompression of the right heart pressure overload and allows an increase in the systemic cardiac output at the expense of lower systemic oxygen saturation.

Long-term follow-up of pulmonary hypertension in CDH

PH typically resolves in most CDH patients within weeks to months of surgical repair; however, there is increasing evidence of its persistence or reoccurrence in patients up to age 12 years, some of whom were clinically asymptomatic [4, 20, 68••, 69••]. The prevalence of PH in CDH survivors is unknown; however, one study suggests it resolves by 5 years of age [23••]. Such findings beg the question: how often, how long, and to what extent should CDH patients be evaluated for ongoing or emerging PH?

There is a paucity of studies investigating the long-term presence and severity of pulmonary vascular disease beyond the first year of life. The evidence regarding recommendations on long-term follow-up is not well delineated in the literature and is mostly suggested by expert opinion based on the prior experience of managing children with other severe cardiopulmonary disorders or single-center retrospective studies [68••, 70••]. Modalities employed to monitor for PH include echocardiogram, EKG, cardiopulmonary exercise testing, biomarker trending, and cardiac catheterization. Echocardiogram may be falsely negative for detecting PH; therefore, because cardiac catheterization remains the gold standard for diagnosing PH, it should be considered in the ongoing evaluation of CDH patients [21••]. In 2008, the American Academy of Pediatrics Section on Surgery and the Committee on Fetus and Newborn provided a template regarding the follow-up of CDH patients after discharge, suggesting echocardiogram and cardiology follow-up every 3 months for the first 18 months, followed by annual evaluation if on supplemental oxygen or if previous echocardiogram was *abnormal* [1]. Subsequently, the American Heart Association and American Thoracic Society, in 2015, suggested class I level of evidence B guidelines for routine evaluation of CDH patients, including longitudinal care in an interdisciplinary PH program and following the recommendations offered for all children with PH [21••]. However, the guidelines do not shed light on the duration, frequency, or complexity of PH surveillance in CDH patients. The guidelines do include class I and IIa levels of evidence C recommendations for follow-up of all patients with PH, particularly regarding

management within a multidisciplinary setting, frequent outpatient follow-up, careful preoperative planning with cardiac anesthesia consultation, and extent of ongoing diagnostic testing.

Some pediatric PH centers report following patients with CDH for the first few years of life, while others report following these patients well into late adolescence. Follow-up in a multidisciplinary setting beyond consultation with a pediatric cardiologist is increasingly more common and may involve ongoing consultation with neonatology, pediatric pulmonology, surgery, gastroenterology, neuropsychology, and nutrition. Beyond echocardiograms and cardiac catheterization, these centers reported the use of lung scintigraphy, cardiopulmonary exercise testing, and measuring brain natriuretic peptide (BNP) levels to evaluate for PH [68••, 71]. Given the possibility that subclinical, potentially significant PH may exist much later in childhood, a balanced follow-up plan should be considered that is not too aggressive but still avoids missing the diagnosis [68••].

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
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