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JACC REVIEW TOPIC OF THE WEEK

Echocardiographic Screening for Pulmonary Hypertension in Congenital Heart Disease

JACC Review Topic of the Week

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ABSTRACT

Echocardiography is the mainstay in screening for pulmonary hypertension (PH). International guidelines suggest echocardiographic parameters for suspecting PH, but these may not apply to many adults with congenital heart disease (ACHD). PH is relatively common in ACHD patients and can significantly affect their exercise capacity, quality of life, and prognosis. Identification of patients who have developed PH and who may benefit from further investigations (including cardiac catheterization) and treatment is thus extremely important. A systematic review and survey of experts from the United Kingdom and Ireland were performed to assess current knowledge and practice on echocardiographic screening for PH in ACHD. This paper presents the findings of the review and expert statements on the optimal approaches when using echocardiography to assess ACHD patients for PH, with particular focus on major subgroups: patients with right ventricular outflow tract obstruction, patients with systemic right ventricles, patients with unrepaired univentricular circulation, and patients with tetralogy of Fallot with pulmonary atresia. (J Am Coll Cardiol 2018;72:2778–88)

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Pulmonary hypertension (PH) is defined as a mean pulmonary arterial (PA) pressure ≥25 mm Hg (1,2) (**Figure 1**). PH is not uncommon in adults with congenital heart disease (ACHD) and significantly affects morbidity and mortality (1,2). ACHD patients with PH have limited exercise capacity, which results in a decreased quality of life (3–5). Moreover, PH often contributes to the development of congestive heart failure and multiorgan failure, increasing the risk for hospitalization and premature death (6,7).

Many patients with congential heart disease (CHD) associated with pulmonary arterial hypertension (PAH) benefit from the introduction of PAH-specific therapies (8–10). Although the evidence is still fairly limited, the use of such therapies was established for patients with Eisenmenger syndrome after the BREATHE-5 (Effects of Tracleer [Bosentan] on Pulmonary Arterial Hypertension Related to Eisenmenger Physiology; NCT00317486) trial, which demonstrated a significant improvement in exercise capacity and functional class using the endothelin receptor antagonist bosentan (8,10). Smaller studies have supported the use of other PAH-specific therapies (including phosphodiesterase-type 5 inhibitors and prostanoids) in patients with Eisenmenger syndrome, whereas patients after defect correction have been included in larger randomized trials, together with patients with idiopathic PAH and connective tissue disease (2,11). Thorough screening of all ACHD is thus crucial in identifying patients who have developed PAH and who could benefit from further investigations, including cardiac catheterization and initiation of PAH-specific therapies.

There are currently no detailed guidelines on how to use echocardiography to screen patients with ACHD for the presence of PAH, especially those with unrepaired or residual defects, and those with complex anatomy. Although international guidelines provide a diagnostic algorithm and a list of supportive echocardiographic signs for all types of PH (12), there are anatomic and physiological considerations that are specific to CHD and thus require additional expertise (**Table 1**) (12). For example, the estimation of the probability of PH in symptomatic patients based on tricuspid regurgitation (TR) velocity, as suggested in the European Society of Cardiology/European Respiratory Society guidelines (12), does not apply to patients with any degree of right ventricular outflow tract obstruction (RVOTO) and/or pulmonary stenosis, or patients with single-ventricle physiology. The same may be true for other echocardiographic signs described in the guidelines that are supportive of the presence of PH (12). For example, flattening of the ventricular septum is also present in patients with pulmonary stenosis or regurgitation, and a pulmonary artery larger than the aorta can be found with intracardiac shunts.

We present an expert statement on the screening for PH in ACHD based on the findings of a survey of experts and a systematic review of available evidence.

ABBREVIATIONS AND ACRONYMS

ACHD = adult congenital heart disease

CHD = congenital heart disease

PA = pulmonary arterial

PAH = pulmonary arterial hypertension

PH = pulmonary hypertension

PH-CHD = pulmonary hypertension associated with congenital heart disease

PR = pulmonary regurgitation

PVR = pulmonary vascular resistance

RV = right ventricle

RVOTO = right ventricular outflow tract obstruction

TR = tricuspid regurgitation

METHODS

The CHAMPION (Congenital Heart disease And pulMonary arterial hyPertension: Improving Outcomes through education and research Networks) Steering Committee (a panel of 4 experts in PH and CHD) identified gaps in published studies, with a particular focus on types of ACHD in which standard echocardiographic markers of PH might not apply. A survey of experts in CHD and PH was then designed to determine how physicians rate the importance of different echocardiographic parameters for raising the suspicion of PH in various clinical scenarios (Online Appendix). A systematic review of all published

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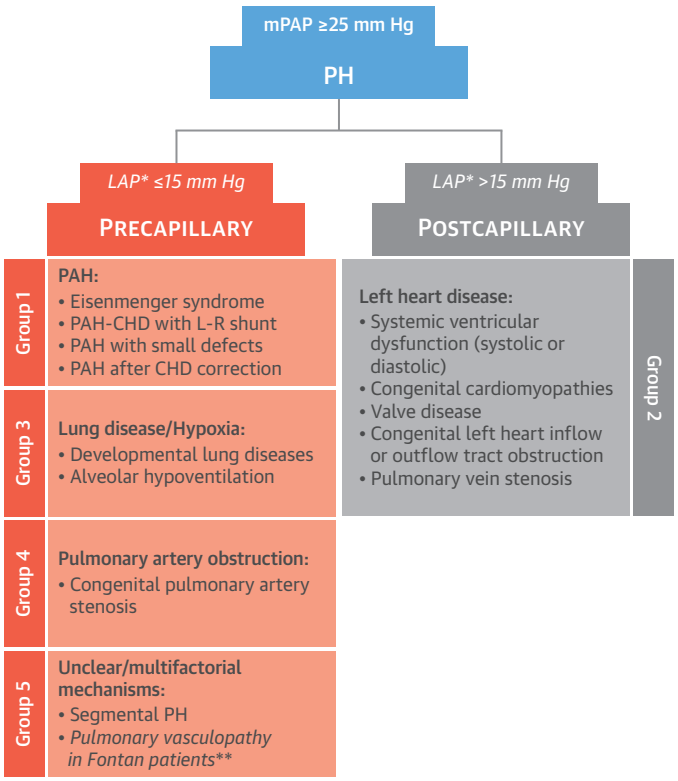
FIGURE 1 CHD Within the PH Clinical Classification Groups



Pulmonary hypertension (PH) is hemodynamically classified into pre- and post-capillary, depending on whether there is an associated rise in left atrial pressure (LAP). The clinical classification of PH defines 5 groups: patients in groups 1, 3, 4, and 5 typically have pre-capillary hemodynamics, whereas group 2 has post-capillary PH. Examples of patients with congenital heart disease (CHD) belonging to each of these groups are reported in the **boxes**. *When a direct LAP cannot be obtained, the pulmonary arterial wedge pressure (PAWP) or left ventricular end-diastolic pressure should be used. **Pulmonary vascular disease may occur in patients after Fontan operation for a univentricular circulation and is likely to affect cardiac output and outcome. However, in the absence of a subpulmonary ventricle, pulmonary pressures cannot rise significantly above 20 mm Hg; hence, the standard definition of PH cannot apply to these patients. Little is known on the pathophysiology and management of this condition; hence, we submit that it should be included in group 5 (PH of unclear or multifactorial mechanisms). mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension.

reports related to the echocardiographic assessment of PH-CHD was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Online Appendix) (13). Preference was given to studies that compared echocardiographic parameters with invasive measures of PA pressures or pulmonary vascular resistance (PVR) and those from the modern era of echocardiography (after 1980). Attributes related to the risk of PH in ACHD were extrapolated from the results of the systematic review and expert opinion of the CHAMPION Steering Committee. The CHAMPION Steering Committee formulated recommendations for each section of this review based on the results of the systematic review and survey. The faculty members critically revised the recommendations. Statistical considerations are presented in the Online Appendix, and the methodology for the systematic review and survey questions are depicted in Online Figures 1 and 2.

RESULTS

SYSTEMATIC REVIEW. Our search methodology identified 512 papers, of which 411 were excluded after title and abstract screening based on the pre-specified exclusion criteria provided in Online Figure 1. The remaining 101 papers underwent full text review. Of these, a further 76 papers were excluded. Reasons for exclusion included no relevant information or no reported correlation to invasive measures of pulmonary pressure. The remaining 25 papers were thoroughly screened for information (Online Figure 3).

SCREENING OF CHD FOR PH. Although the recommended follow-up varies for different types of ACHD based on factors such as the underlying anatomy, previous repair, and residual lesions, it is widely accepted that PH should be considered and investigated in all ACHD practices, during both baseline assessment and lifelong follow-up. However, the systemic review identified no data that provided guidance on the frequency of screening of CHD patients for PAH.

Expert statement. Regular screening of CHD patients for the development of PH is recommended, the frequency of which depends on the underlying anatomy. Screening for PH should occur at each echocardiographic assessment, including patients with repaired defects, although data on the specificity and sensitivity of echocardiographic parameters in ACHD patients with more complex anatomy are scarce. Patients with signs of PH require further investigations, including cardiac catheterization, to establish the diagnosis.

WHICH ECHOCARDIOGRAPHIC PARAMETERS APPLY IN SCREENING ACHD PATIENTS FOR PH? Survey responses on the echocardiographic parameters routinely used in clinical practice and conditions in which standard parameters did not apply are presented in the Online Appendix.

Our systematic review yielded a small number of papers that validated echocardiographic parameters against cardiac catheterization in different CHD types. The TR gradient and acceleration time of the right ventricular outflow tract (RVOT) Doppler were most commonly assessed in patients with no obstruction to pulmonary blood flow (14–23). A good correlation was shown between invasive PVR and pulmonary

TABLE 1 Echocardiographic Parameters and Signs Suggestive of PH*: Considerations for Patients With ACHD

Parameter	Comments Related to ACHD	Parameters Do Not Apply In:
Peak TR velocity/gradient	Assumes that: The RV is directly communicating with the pulmonary circulation (see pulmonary atresia); There is no RVOTO or peripheral pulmonary stenosis RA pressure is adequately estimated and added to the TR gradient	Pulmonary atresia Pulmonary stenosis (valvular, subvalvular, or supravalvular) Double-chambered RV Torrential TR, in which the Bernoulli equation does not apply
Ventricles RV/LV basal diameter ratio Eccentricity index (systolic and/or diastolic)	Assumes that: There is biventricular circulation There is no other cause for pressure (or volume) overload to the RV (or to the LV in patients with a systemic RV)	Univentricular hearts, both unrepaired and repaired (Fontan circulation) Pulmonary stenosis Double-chambered RV ccTGA or post-atrial switch for transposition of great arteries Atrial septal defects
PA RV outflow Doppler acceleration time/midsystolic notching Early PR velocity PA diameter	Assumes that: There is no RVOTO There is no other cause for PA dilatation (e.g., a left-to-right shunt), pulmonary stenosis/regurgitation, congenitally abnormal PA	Pulmonary stenosis Absent pulmonary valve syndrome Severe PR Atrial septal defects
Inferior vena cava Diameter Inspiratory collapse RA area	Assumes that: There is no other cause for raised RA pressure (e.g., tricuspid valve disease, left-to-right shunt, restrictive RV physiology)	Tricuspid stenosis or severe regurgitation Pulmonary stenosis Restrictive RV physiology in tetralogy of Fallot Atrial septal defects Persistent RA dilation after repair of the defect or arrhythmia (atrial fibrillation)

*As recommended by European Society of Cardiology/European Respiratory Society Guidelines (12).

ACHD = adult congenital heart disease; ccTGA = congenitally corrected transposition of the great arteries; LV = left ventricle; PA = pulmonary artery; PH = pulmonary hypertension; PR = pulmonary regurgitation; RA = right atrial; RV = right ventricle; RVOTO = right ventricular outflow tract obstruction; TR = tricuspid regurgitation.

regurgitation (PR) parameters on echocardiography (24). Murphy et al. (25) validated the ventricular septal defect shunt gradient as a means of estimating pulmonary and/or systemic vascular resistance against invasive hemodynamics, although a few papers used this gradient to estimate PA pressures (subtracted from systolic aortic pressure, in the absence of RVOTO) (25–28). The relationship between right ventricular (RV) function (expressed as the tricuspid annulus plane systolic excursion [TAPSE]) and PH-CHD was demonstrated in children (29), whereas tissue Doppler parameters were less helpful (29–31). Several other echocardiographic parameters were assessed, and the TR gradient and the peak systolic velocity of the tricuspid annulus were identified as the strongest predictors of PVR, but correlation with invasive measures was moderate for the former and weak for the latter (31). Few papers addressed the issue of ventricular–ventricular interaction and the movement of the ventricular septum in biventricular hearts (32,33). A good correlation was found between hepatic venous Doppler characteristics (reflecting right atrial hemodynamics and the diastolic properties of the RV, dominant A-wave) and invasive PA pressure (34).

Although echocardiographic equations for calculating PVR are available for patients without CHD, the anatomic complexity and lack of accuracy in assessing left atrial pressure and the filling pressure of the systemic ventricle limit their applicability in ACHD. We submit that it is best to focus on "simple" echocardiographic markers of PH in routine ACHD practice and to refer patients to cardiac catheterization when suspicion of PH is raised.

Expert statement. Many standard echocardiographic parameters for the assessment of PH in patients without CHD do not apply to patients with CHD and should not be used without a good understanding of the underlying cardiac anatomy (**Central Illustration**). Training and expertise specific to PH-CHD is paramount for the performance and interpretation of echocardiograms. Further studies are required to assess whether the cutoffs that are recommended for use in the general population (12) apply in CHD, with a focus on maximizing sensitivity (reducing false negatives) to avoid delays in diagnosis. This should always be weighed against the (current) low risk of cardiac catheterization.

IMPORTANCE OF ECHOCARDIOGRAPHIC PARAMETERS IN SUSPECTING THE PRESENCE OF PH IN SPECIFIC CHD CONDITIONS. Participants were asked to describe how significant various selected echocardiographic parameters were in raising the suspicion of PH in each of the following conditions: RVOTO and/or pulmonary stenosis; unrepaired and/or palliated complex pulmonary atresia; univentricular circulation (e.g., double-inlet left ventricle); and a Mustard or Senning procedure for transposition of the great arteries. **Figure 2** shows schematics of the conditions covered

CENTRAL ILLUSTRATION **Suspicion of Pulmonary Hypertension in Specific CHD Conditions**

	Congenital Heart Disease (CHD) Condition			
	Right ventricular outflow tract obstruction or pulmonary stenosis	Complex pulmonary atresia in tetralogy of Fallot (unrepaired)	Unrepaired univentricular circulation	Transposition of the great arteries after atrial redirection operation: Mustard or Senning
Anatomic considerations in pulmonary hypertension (PH) screening	• Tricuspid regurgitation (TR) gradient ≠ pulmonary arterial (PA) pressure. • Right ventricle/left ventricle diameter ratio, PA and right atrial (RA) size are altered.	• Neither TR nor mitral regurgitation (MR) Doppler will diagnose PH. • Identifying segmental PH by echocardiographic means is difficult.	• Neither TR nor MR Doppler will diagnose PH.	• TR gradient will not diagnose PH.
Adapted PH screening	• Evaluate the forward velocity/gradient across the pulmonary valve, in conjunction with the TR velocity/gradient. • Peak Doppler velocity across systemic-pulmonary collateral vessels. • Pulmonary regurgitation (PR) gradient may be affected by significant PS.	• PA dilatation of hypertensive segments could be a marker of PH. • Doppler interrogation of Blalock-Taussig shunts and collateral vessels provides useful data in estimating PA pressures. • Large caliber collateral vessels to the lung indicate PH.	• PR gradient and gradient across systemic-to-pulmonary shunts indicates pressure gradient between the aorta and PA. Low gradient may suggest PH • Low gradient across the pulmonary valve is suggestive of PH when the PA is connected to a systemic ventricle.	• PR and MR gradient, increased size of the PAs, plus the forward flow across the pulmonary valve may suggest PH. • Progressive dilation of the sub-pulmonary left ventricle may be a sign of PH.

Dimopoulos, K. et al. J Am Coll Cardiol. 2018;72(22):2778-88.

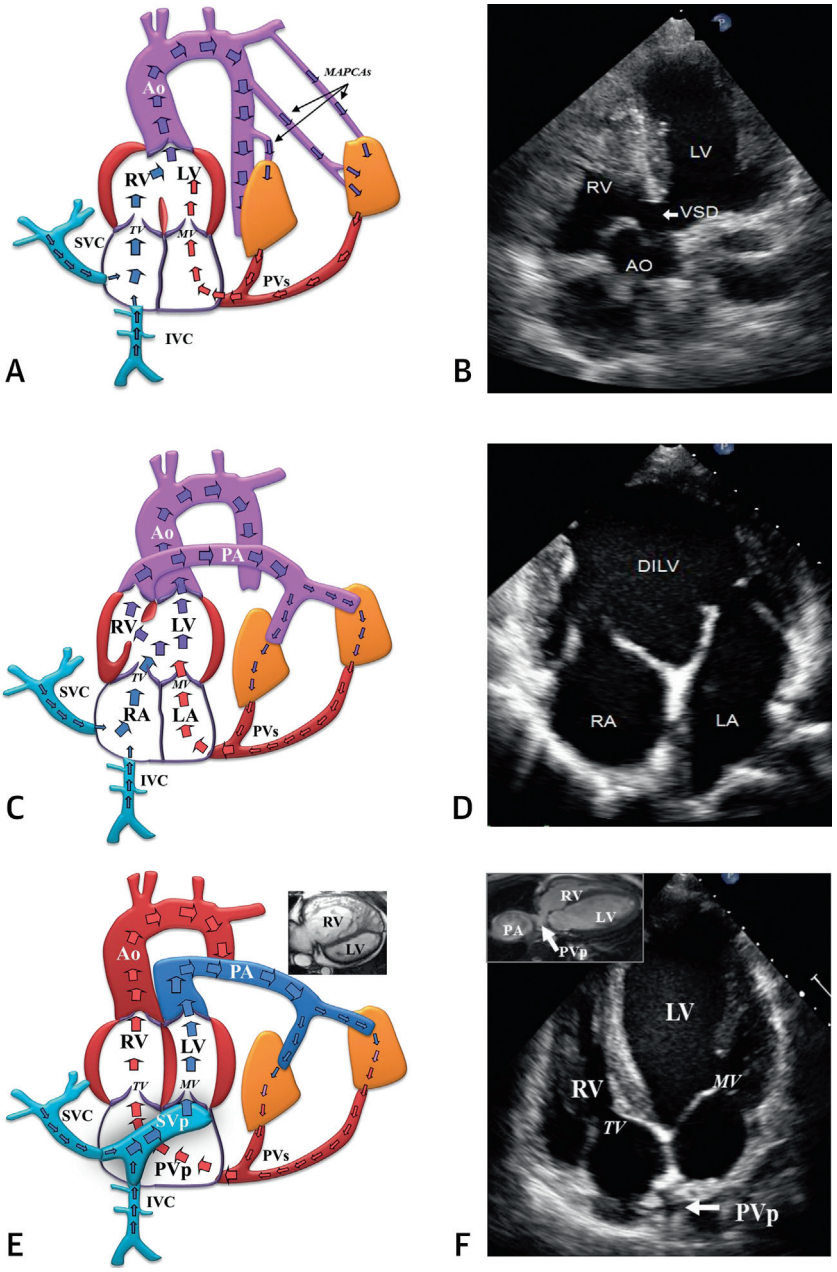
Standard markers of pulmonary hypertension (PH) often do not apply in congenital heart disease (CHD) or need to be adjusted for the underlying anatomy. Therefore, different factors need to be taken into consideration when PH is suspected in each specific CHD condition.

in this review, and Figure 3 shows an additional schematic of a patient with RVOTO.

RVOTO AND/OR PULMONARY STENOSIS. This group includes valvular, subvalvar (RVOTO), and supravalvular stenosis. Depending on the severity of the stenosis, there might be a mild to severe pressure gradient between the RV and the pulmonary artery. This must be considered when using echocardiography to assess RV pressure and PA pressure in patients with biventricular physiology.

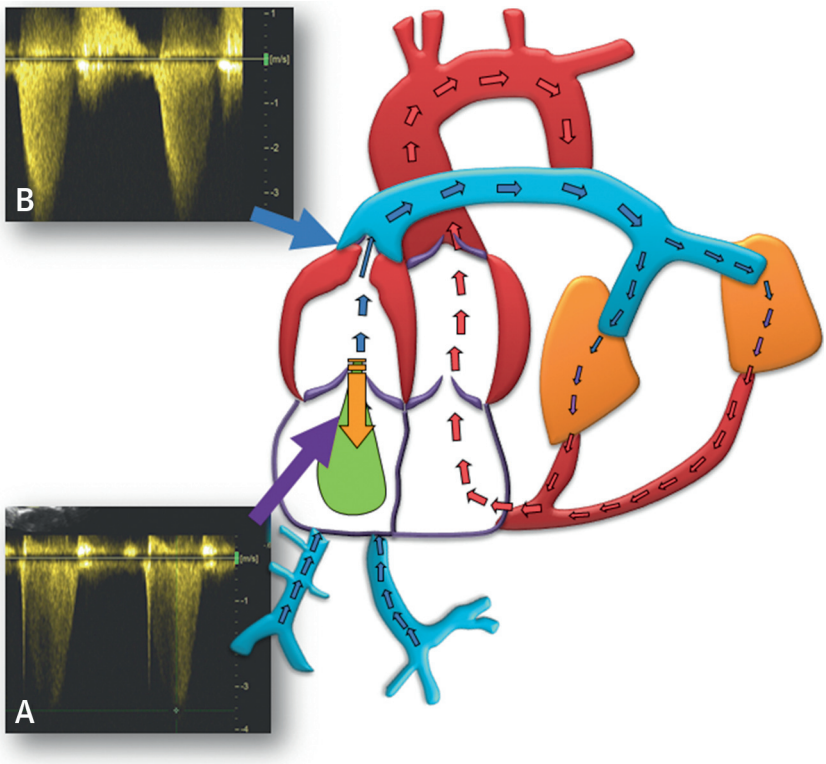
The survey results supported the use of the PR gradient in this condition, as well as the peak Doppler velocity across systemic pulmonary collateral vessels when these are present and detectable. The survey

FIGURE 2 Examples of CHD in Which Standard Echocardiographic Criteria for the Detection of PH Do Not Apply



(A and B) Complex pulmonary atresia in tetralogy of Fallot. Note that lung perfusion is achieved via major aortopulmonary collateral arteries (MAPCAs) **(thin black arrows)** and a patent ductus arteriosus (if present) to different areas of the lungs. **(C and D)** Univentricular circulation in unrepaired double-inlet left ventricle (LV). Note that both atrioventricular valves are connected to a large LV, whereas the right ventricle (RV) is typically hypoplastic and communicating with the LV ventricle through a ventricular septal defect (VSD). Depending on the ventriculo-arterial arrangement (normal or transposed), the LV may be connected to either the aorta (Ao) (depicted here) or the pulmonary artery (PA). In the absence of significant pulmonary stenosis, pulmonary vascular disease is likely to develop. **(E and F)** Atrial switch repair for transposition of great arteries (Mustard procedure). Note the systemic venous pathways (SVp) redirecting systemic venous blood toward the subpulmonary, morphologically LV and the PA; the pulmonary venous pathway (PVp) is redirecting pulmonary venous (PV) blood toward the systemic RV. In the absence of PH or significant pulmonary stenosis, the systemic RV is typically dilated and hypertrophied, whereas the subpulmonary LV is small and the ventricular septum is deviated towards the LV **(E, inset)**. However, if severe PH develops **(F)**, the LV may dilate and appear dominant again, with deviation of the ventricular septum towards the RV. The **inset in F** is a cardiac magnetic resonance frame from the same patient, with a very dilated PA and dilated subpulmonary LV. CHD = congenital heart disease; DILV = double-inlet left ventricle; IVC = inferior vena cava; LA = left atrial; MV = mitral valve; RA = right atrial; TV = tricuspid valve; SVC = superior vena cava; other abbreviations as in Figure 1.

FIGURE 3 Example of a Patient With RVOTO



In this case, there is moderate right ventricular outflow tract obstruction (RVOTO) **(blue arrow)**. Tricuspid regurgitation (TR) velocity is raised **(A)**, suggesting a rise in right ventricular (RV) systolic pressure (estimated at 52 mm Hg plus right atrial pressure). However, pulmonary arterial (PA) pressure is not raised, because there is a moderate pulmonary stenosis with a peak gradient of 45 mm Hg, which appears to be sufficient to explain the rise in RV pressure **(B)**. Therefore, when assessing patients for pulmonary hypertension using the TR Doppler, it is essential to identify and account for RVOTO and/or pulmonary stenosis. This can be achieved echocardiographically, that is, the RVOT and pulmonary valve should be interrogated routinely in patients with suspected PH. Moreover, the presence of an ejection systolic murmur over the pulmonary area on cardiac auscultation should raise the suspicion of RVOTO.

data also highlighted the importance of evaluating the forward velocity and/or gradient across the pulmonary valve in conjunction with the TR velocity and/or gradient when assessing patients with RVOTO for PH (Online Figure 4).

The systematic review identified several studies that assessed the diagnostic accuracy of the TR gradient and pulmonary velocity acceleration time parameters in CHD in which patients with any RVOTO were explicitly excluded (17,19,21,22). No strong evidence was identified in any other papers, neither for the use of PR Doppler nor on how to adjust estimates of PA pressure from the TR gradient in patients with an RVOT gradient.

Expert statement. In patients with RVOTO, it is essential to recognize that the TR gradient does not directly reflect PA pressure, but rather the RV systolic pressure, which is the result of the RVOTO plus the PA pressure (Figure 3). The difference between the pressure gradient calculated using TR velocity and RVOT velocity reflects the systolic PA pressure. In patients with shunts between the pulmonary artery and the aorta (Blalock-Taussig, Waterston, patent ductus arteriosus), the peak Doppler gradient across the shunt may provide an estimate of PA pressure (accounting for systemic pressures, which can be measured using a sphygmomanometer). In practice, however, such shunts may not be easy to detect and adequately interrogated with echocardiography. The ratio between the right and left ventricular diameters, and PA and right atrial size are likely to be influenced by the presence of the RVOTO and cannot be used to assess for the presence of PH (Table 2).

COMPLEX PULMONARY ATRESIA IN TETRALOGY OF FALLOT (UNREPAIRED). Pulmonary atresia with a ventricular septal defect is at the extreme end of the

spectrum of tetralogy of Fallot. Within pulmonary atresia, there is a wide variety of conditions, depending on the anatomy of the pulmonary arteries, which range from confluent branch pulmonary arteries to complex forms in which there is complete or near-complete absence of the pulmonary arteries (35). Blood supply to the lungs typically occurs through a patent ductus arteriosus and/or major aortopulmonary collateral vessels, which, when large, can allow excessive flow to the segment of the lung supplied, and hence, trigger the development of pulmonary vascular disease, which is typically segmental (i.e., affecting certain, but not all lung segments) (**Figure 1**). There are limited data to suggest that PAH-specific therapies may be beneficial in these patients; hence, the identification of PH in pulmonary atresia is essential (36,37).

The survey data demonstrated an understanding that neither TR nor mitral regurgitation Doppler imaging are useful in diagnosing segmental PH (most likely because there is no direct connection between the ventricles and the pulmonary vascular tree). Doppler-derived gradients across collateral vessels to various lung segments can be useful in identifying potential areas of pulmonary vascular disease, where a lower than expected pressure gradient between the aorta and lung vessels might be encountered. Moreover, PA dilation in hypertensive segments was believed to be a potential marker of PH (Online Figure 4).

The systematic review identified no studies that assessed echocardiographic parameters for the diagnosis of PH in complex pulmonary atresia. Doppler interrogation of Blalock-Taussig shunts was shown to provide useful information in estimating PA pressures in patients with complex CHD (including 1 patient with congenitally corrected [L-]transposition of the great arteries and pulmonary atresia), and the same concept should apply to collateral vessels in pulmonary atresia (38). Schuuring et al. (39), who described 7 patients with segmental PH treated successfully with PAH-specific therapies, provided no echocardiographic features.

Expert statement. Identification of segmental PH by echocardiographic means is difficult and requires clinical suspicion. The Doppler gradient across collateral vessels identified during echocardiography can raise the suspicion of PH in the respective lung segment. Moreover, identification of PA (or collateral vessel) dilation or large-caliber collateral vessels to the lung can also point toward PH. Parameters related to the ventricles or atria, and Doppler gradients across valves are unrelated to PH in unrepaired pulmonary atresia (**Table 2**).

TABLE 2 Summary of Expert Opinion for the Echocardiographic Diagnosis of PH in CHD Patients

Condition/Anatomy	Summary of Expert Opinion
Pulmonary stenosis/RVOTO	Peak TR gradient reflects RV systolic pressure (the result of RVOTO and PAP), not just PA pressure Peak Doppler gradient across shunts between the PA and aorta can provide rough estimates of PA pressure, when present and visible on echocardiography RV/LV basal diameter ratio cannot be used to assess the presence of PH
Unrepaired/palliated complex pulmonary atresia	Clinical suspicion is required in addition to echocardiography The following parameters can raise suspicion of PH: A low peak Doppler velocity across collateral vessels or shunts PA (or collateral vessel dilatation) or large-caliber collateral vessels The following parameters are unrelated to PH: Peak Doppler gradients across valves Parameters relating to ventricles/atria
Univentricular circulation (e.g., DILV)	In adult patients with no pulmonary stenosis, PH diagnosis can be made with a high degree of certainty using echocardiography, by confirming the intracardiac anatomy and unprotected pulmonary circulation
Mustard or Senning procedure for TGA	The following parameters should be used routinely: Systolic MR gradient Peak PR gradient Increased size of the PAs Eccentricity index should not be used, but progressive dilatation of the subpulmonary LV should raise the suspicion of PH Post-capillary PH is common in patients with a systemic RV due to RV dysfunction, TR and/or pulmonary venous pathway obstruction; all patients should undergo cardiac catheterization to differentiate between pre- and post-capillary PH

CHD = congenital heart disease; DILV = double inlet left ventricle; MR = mitral regurgitation; PAP = pulmonary arterial pressure; TGA = transposition of the great arteries; other abbreviations as in Table 1.

UNREPAIRED UNIVENTRICULAR CIRCULATION. Functional univentricular hearts occur in those in which there is a predominant ventricle, and typically, a small (rudimentary) ventricle that is not amenable to biventricular repair. Both the pulmonary artery and aorta can be exposed to systemic pressures (40,41) (tricuspid or mitral atresia, double inlet left or right ventricle). PH may develop in these patients when the pulmonary circulation is unprotected or partially protected (no and/or mild to moderate pulmonary stenosis).

The survey highlighted the nonapplicability of TR and mitral regurgitation Doppler gradients in this condition, in which the atrioventricular valve(s) provide information on the pressures in the systemic ventricle, but not necessarily in the pulmonary circulation. The PR gradient and the gradient across systemic-to-pulmonary shunts (patent ductus arteriosus or surgical shunts, such as Blalock-Taussig, Potts, or Waterston shunts) was considered significant. The latter provides an indication of the pressure gradient between the aorta and the pulmonary artery, and when the gradient is low, it may suggest PH (Online Figure 4).

The survey results were supported by 1 paper identified in the systematic review, which assessed the ability of echocardiography to assess PA pressures in unrepaired or palliated univentricular hearts. Chaudhari et al. (38) demonstrated that Doppler interrogation of Blalock-Taussig shunts could accurately predict PA pressures and pulmonary blood flow in complex CHD. This concept might apply to a patent ductus arteriosus or other surgical shunts, such as Potts or Waterston.

Expert statement. Expertise is required when assessing patients with unrepaired or palliated univentricular hearts. In adult patients with no pulmonary stenosis (including subpulmonary stenosis due to a small ventricular septal defect in concordant atrioventricular arrangement), and hence, no pressure gradient between a systemic ventricle and the pulmonary arteries, the diagnosis of severe PH can be made with a high degree of certainty on echocardiography. Echocardiographic estimates of the PR peak gradients and the gradient across the pulmonary valve or systemic-to-pulmonary shunts are also helpful when screening patients with unrepaired univentricular circulation for PH (**Table 2**).

TRANSPOSITION OF THE GREAT ARTERIES AFTER ATRIAL REDIRECTION OPERATION: MUSTARD OR SENNING. Patients with transposition of the great arteries who have undergone atrial re-direction procedures are left with a morphological RV in the systemic position and a morphological left ventricle in the subpulmonary position. PH can develop in these patients, even after timely repair of the defect and closure of a ventricular septal defect; these patients may benefit from PAH-specific therapy, although data are limited (42,43). More commonly, post-capillary PH develops due to RV dysfunction, significant TR, or pulmonary venous pathway obstruction.

Our survey of experts highlighted the anatomic particularities of this condition. In particular, mitral regurgitation (rather than TR) might be used to estimate systolic pressure in the subpulmonary ventricle as well as PA pressures, accounting for any outflow tract obstruction. Moreover, respondents highlighted the role of the PR gradient, pulmonary velocity Doppler, size of the pulmonary artery, and the behavior of the ventricular septum (Online Figure 4).

The systematic review found no papers that assessed echocardiographic parameters against invasive values of PA pressure in this population. Ebenroth et al. (43) described a case series of 93 patients who underwent a Mustard procedure; of the 8 patients (13%) who had a PA pressure >50% systemic, 4 had anatomic explanations for this: 3 had "baffle" (pathway) obstruction and 2 had left lung hypoplasia (43). The investigators listed the echocardiographic parameters used to suspect PH or raised subpulmonary ventricular pressures: shift of the ventricular septum toward the systemic RV; elevated PR end-diastolic velocity; or elevated mitral regurgitation velocity (43).

Expert statement. The following parameters should be routinely used to raise the suspicion of PH in patients who have undergone Mustard and/or Senning procedures: mitral regurgitation gradient; PR gradient; and increased size of the pulmonary arteries, as well as the characteristics of the forward flow across the pulmonary valve. The eccentricity index cannot be used as recommended by the guidelines, but a shift toward the systemic RV and progressive dilation of the subpulmonary left ventricle (in the absence of severe pulmonary stenosis and/or regurgitation, or significant baffle leak) may be a sign of PH. Cardiac catheterization is essential in differentiating between pre- and post-capillary PH, and anatomic causes of PH (e.g., baffle or pathway obstruction) should be excluded (**Table 2**).

DISCUSSION

Routine screening for PH is recommended in all patients with CHD undergoing echocardiography. Echocardiography remains a fundamental part of the routine assessment of all CHD patients, and routine echocardiographic assessment should follow a protocolized approach that includes screening for PH. Standard markers of PH often do not apply in CHD or need to be adjusted according to the underlying anatomy. Strict guidelines for PH-CHD are difficult because of the lack of strong evidence; however, recommendations can be provided based on available evidence and expert consensus.

In this review, we provided guidance based on the findings of a systematic review of published studies and the results of a survey of experts. Echocardiography cannot be a substitute for cardiac catheterization in most cases, with the exception, perhaps, of some adult cyanotic patients with large post-tricuspid shunts. It can, however, provide relevant information that, together with the clinical picture, can raise the suspicion of PH and aid management (14). PH should be identified promptly in CHD patients, because PH has a significant impact on functional capacity, quality of life, and outcome. PH-CHD patients often benefit from PAH-specific therapies, although evidence is limited mainly to patients with Eisenmenger syndrome in functional class III and to patients with repaired defects and PAH. The consensus

recommendations from this study should be validated in large studies and registries, and updated as new evidence and new imaging modalities emerge (32,44,45). ACHD is a vastly heterogeneous population, and providing a standardized approach that applies to each individual case is impossible. There are numerous potential pitfalls, and correct interpretation requires an understanding of each patient's particular characteristics, as well as significant expertise in CHD and PH.

The role of noninvasive screening for PH is to identify patients who have an increase in PA pressures and who would therefore benefit from cardiac catheterization. Cardiac catheterization is the only way to distinguish between pre- and post-capillary PH and to measure PVR reliably, while other investigations are required to exclude other causes of PH (e.g., lung disease and/or hypoxia, chronic thromboembolic disease). Moreover, PH-CHD may also be simply related to high pulmonary blood flow in the presence a large left-to-right shunt, which may be difficult to appreciate on echocardiography. Finally, there is limited evidence on the use of targeted PAH therapies in patients with ACHD and PH who do not have Eisenmenger syndrome with simple defects (atrial or ventricular septal defect) or repaired CHD.

STUDY LIMITATIONS

This work has important limitations that are primarily related to the extremely limited published studies (in terms of number of papers and quality of evidence) to support practice and to define the sensitivity and, especially, the specificity, of echocardiographic parameters in these rare conditions. The primary scope of the search was to inform expert opinion and statements, rather than to provide entirely evidence-based recommendations. In the absence of validated diagnostic tools, expert judgment should be used to identify patients with PH by combining echocardiographic signs with the previous probability of PH based on anatomy, type, and time of previous surgery, and other clinical parameters (e.g., presence of Down syndrome).

The survey of experts was aimed at understanding modern practice in specialist centers, but had limited influence on expert statements. Studies that compare echocardiographic parameters to the gold standard of cardiac catheterization in various ACHD cohorts and a wide range of pulmonary pressures and resistances, also incorporating previous probability based on clinical information, are urgently needed to inform clinical practice. Efforts should be made to achieve homogenization of the assessment of PH in ACHD as well as selection of proper methodologies of correlation with invasive measurements and other noninvasive cardiovascular imaging in multicenter studies and clinical trials. This would also open the way to future lines of physiological and basic science investigations.

CONCLUSIONS

All patients with CHD should undergo regular assessment for the presence of PH during routine echocardiography, as should patients with clinical suspicion of PH. This should occur in centers with adequate expertise in the management of both PH and CHD. The paucity of evidence to guide the echocardiographic assessment urgently calls for registries and studies that will provide support to clinical practice.

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APPENDIX For expanded Methods and Results sections as well as supplemental figures, please see the online version of this paper.