Review Article

Pulmonary hypertension in adults with congenital heart defects (ACHDs)—in light of the 2022 ESC PAH guidelines—part I: definition, epidemiology, classification, diagnostics, genetics, risk stratification and follow-up, gender aspects

Harald Kaemmerer[1], Gerhard Paul Diller[2], Ingo Dähnert[3], Stephan Achenbach[4], Christina A. Eichstaedt[5,6,7], Andreas Eicken[1], Annika Freiberger[1], Sebastian Freilinger[1], Ralf Geiger[8], Matthias Gorenflo[9], Ekkehard Grünig[5,7], Alfred Hager[1], Michael Huntgeburth[1], Ann-Sophie Kaemmerer-Suleiman[10], Rainer Kozlik-Feldmann[11], Astrid E. Lammers[12], Nicole Nagdyman[1], Sebastian Michel[13,14], Kai Helge Schmidt[15], Mathieu Suleiman[10], Anselm Uebing[16,17], Fabian von Scheidt[1], Ulrike Herberg[18], Christian Apitz[19]

[1]International Center for Adults with Congenital Heart Defects, Clinic for Congenital Heart Defects and Pediatric Cardiology, Deutsches Herzzentrum München, TUM University Hospital, Munich, Germany; [2]Department of Cardiology III: Congenital Heart Malformations (ACHD) and Valve Diseases, University Hospital Münster, Albert-Schweitzer-Campus 1, Münster, Germany; [3]University Clinic for Pediatric Cardiology, Heart Center Leipzig, Leipzig, Germany; [4]University Hospital Erlangen, Medizinische Klinik 2 - Kardiologie und Angiologie, Erlangen, Germany; [5]Center for Pulmonary Hypertension, Thorax Clinic Heidelberg at Heidelberg University Hospital, Heidelberg, Germany; [6]Institute of Human Genetics, Heidelberg University, Heidelberg, Germany; [7]Translational Lung Research Center Heidelberg (TLRC), German Center for Lung Research (DZL), Heidelberg, Germany; [8]Department of Pediatrics III, Cardiology, Pneumology, Allergology, Cystic Fibrosis, Innsbruck, Austria; [9]Department of Pediatric Cardiology and Congenital Heart Defects, Heidelberg University Hospital, Heidelberg, Germany; [10]Department of Cardiac Surgery, Erlangen University Hospital, Erlangen, Germany; [11]Clinic and Polyclinic for Pediatric Cardiology, Hamburg University Heart and Vascular Center, Clinic and Polyclinic for Pediatric Heart Medicine and Adults with Congenital Heart Defects, Hamburg, Germany; [12]Department of Pediatric Cardiology, University Hospital Münster, Albert-Schweitzer-Campus 1, Münster, Germany; [13]Division for Congenital and Pediatric Heart Surgery, Department of Cardiac Surgery, Ludwig Maximilian University Munich, Campus Großhadern, Munich, Germany; [14]Comprehensive Pneumology Center Munich, German Center for Lung Research (DZL), Munich, Germany; [15]University Medical Center Mainz, Center for Cardiology - Cardiology I, Johannes Gutenberg University Mainz, Mainz, Germany; [16]University Hospital Schleswig-Holstein, Clinic for Congenital Heart Defects and Pediatric Cardiology, Kiel, Germany; [17]German Centre for Cardiovascular Research (DZHK), Partner Site Kiel, Kiel, Germany; [18]Department of Pediatric Cardiology (U.H.), Medical Faculty, Rheinisch-Westfälische Technische Hochschule Aachen University, Aachen, Germany; [19]Department of Pediatric Cardiology, University Hospital for Pediatrics and Adolescent Medicine Ulm, Ulm, Germany

Contributions: (I) Conception and design: H Kaemmerer, C Apitz, GP Diller, E Grünig; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Dr. Harald Kaemmerer, MD, VMD. International Center for Adults with Congenital Heart Defects, Clinic for Congenital Heart Defects and Pediatric Cardiology, Deutsches Herzzentrum München, TUM University Hospital, Lazarettstr. 36, 80636 Munich, Germany. Email: kaemmerer@dhm.mhn.de.

Abstract: The number of adults with congenital heart defects (ACHDs) is steadily increasing and is about 360,000 in Germany. Congenital heart defect (CHD) is often associated with pulmonary hypertension (PH), which sometimes develops early in untreated CHD. Despite timely treatment of CHD, PH not infrequently persists, redevelops in older age, and is associated with significant morbidity and lethality. The revised European Society of Cardiology (ESC)/European Respiratory Society (ERS) 2022 guidelines for the diagnosis and treatment of PH represent a significant contribution to the optimized care of those affected. However, the topic of "adults with congenital heart defects" is treated only relatively superficially in this context. In the present article, part I, therefore, this topic is commented on in detail from the perspective of congenital cardiology with a special focus on definition, epidemiology, classification, diagnostics, genetics,

risk stratification and follow-up and gender aspects of PH in ACHDs. This paper consists of two parts. Part II will provide comments on the topics of supportive therapy, special situations like pregnancy, contraception, and non-cardiac surgery, targeted pharmacotherapy, organ transplantation, special management like shunt lesion, left ventricular disease, and univentricular hearts, interventions, intensive care, ACHDs follow-up and future perspective on PH in ACHDs. By examining these aspects in detail, this article aims to fill the gaps in the existing guidelines and provide a more thorough understanding from the perspective of congenital cardiology.

Keywords: Pulmonary arterial hypertension (PAH); congenital heart disease; Eisenmenger syndrome

Submitted Apr 03, 2024. Accepted for publication Sep 13, 2024. Published online Oct 22, 2024.
doi: 10.21037/cdt-24-148
View this article at: https://dx.doi.org/10.21037/cdt-24-148

Introduction

Congenital heart defects (CHDs) are the most common isolated congenital organ anomaly. Worldwide, approximately 1.5 million children are born with CHD per year, in Germany approximately 8,500 (1,2). Due to improved medical care in the industrialized world, more than 95% of them reach adulthood. Worldwide, there are currently about 50 million adults living with congenital heart diseases (ACHDs), in Germany about 360,000 (3,4). One of the most important complications of CHD is pulmonary hypertension (PH) or pulmonary vascular disease (PVD), which can develop at any age (5).

The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) 2022 revised the 2015 ESC and ERS guidelines. They include the hemodynamic definition of PH clinical classification, diagnostic strategies, risk assessment, risk-stratified therapy, specifics of left heart, pulmonary disease, hypoxia, chronic thromboembolic PH (CTEPH), and their care by a multidisciplinary team working with patient associations and engaging in research, teaching, and education (6,7). Because little space is given to PH in ACHDs in this context, the present article aims to provide important additional information on this constellation of problems (8-10).

Definition of pulmonary arterial hypertension (PAH)

The definition of PH and its various forms is based on hemodynamic parameters obtained by cardiac catheterization at rest and in the supine position. Although hemodynamics represent the central element for characterizing PH, the definitive diagnosis and classification of PH should reflect the entire clinical context and take into account the results of all examinations.

PH is defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg at rest (*Table 1*), according to the 2022 ESC/ERS guidelines.

In precapillary PH, it is important to include pulmonary vascular resistance (PVR) and pulmonary arterial wedge pressure (PAWP) in the definition to distinguish increased pulmonary arterial pressure (PAP) due to PVD from increased PAP due to left heart disease (LHD), and from increased pulmonary blood flow (*Table 1*).

Based on the available data, the upper limit of normal PVR and the lowest prognostically relevant threshold of PVR were set at ~2 Wood units (WU) (11-14). PVR relates to body surface area and age, and higher PVR values may exist in healthy elderly individuals.

Of particular note in the current ERS/ESC-PH guideline, especially for adults with shunt lesions in the setting of CHD, is the definition of "unclassified PH": there are patients with elevated mPAP (>20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg). These patients are often characterized by increased pulmonary blood flow and, although they have PH, do not meet the criteria for pre- or postcapillary PH. In this case, "unclassified PH" is present according to the current ESC/ERS guideline.

Patients with increased pulmonary blood flow due to shunt vitium in CHD may fall under this definition.

Epidemiology and classification of PAH

PH is an important health problem with a worldwide PH prevalence of approximately 1% (9,15). Of adults with CHD, approximately 3–7% develop PAH during their lifetime, especially women. The incidence depends largely on the type of underlying CHD and increases with patient age

Table 1 Hemodynamic definitions of pulmonary hypertension according to the 2022 ESC/ERS guidelines (9)

Definition	Hemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg
	PAWP ≤15 mmHg
	PVR >2 WU
IpcPH	mPAP >20 mmHg
	PAWP >15 mmHg
	PVR ≤2 WU
CpcPH	mPAP >20 mmHg
	PAWP >15 mmHg
	PVR >2 WU
Exercise-induced PH ("exercise PH")	mPAP/CO slope between rest and stress >3 mmHg/L/min

Some patients have elevated mPAP (>20 mmHg) but low PVR (≤2 WU) and low PAWP (≤15 mmHg); this hemodynamic state can be described by the term "unclassified PH" (see text for further details). ESC/ERS, European Society of Cardiology/European Respiratory Society; PH, pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; WU, Wood units; IpcPH, isolated postcapillary pulmonary hypertension; CpcPH, combined post- and precapillary pulmonary hypertension; CO, cardiac output.

and age at defect closure (16). After correction of a simple heart defect, the estimated PAH prevalence is 3% (17). Eisenmenger syndrome, the most severe form of PAH in CHD, is decreasing in industrialized countries. While fewer patients with simple CHD treated early will develop PAH in adulthood in the future, more patients with PAH in complex CHD are expected to develop PAH in adulthood and those who continue to develop PAH decades after defect closure (18). In addition, patients who develop PH because of concomitant cardiac and noncardiac diseases, e.g., LHD or chronic obstructive pulmonary disease (COPD), portal hypertension infectious diseases [schistosomiasis, human immunodeficiency virus (HIV)], and living at high altitudes (15).

Also in the current 2022 ESC guidelines, the PH classification is based on the proposals of the previous World Conferences or World Symposia. The assignment of patients to this classification is therapeutically important (7,9) (*Table 2*). Patients with PH in CHD appear in this classification preferably in groups 1 and 2. However, it must be noted that adults with CHD are then also assigned to classes 3, 4, and 5 with increasing age depending on comorbidities (19).

Specific changes in the new classification include the subdivision of idiopathic PAH (IPAH) group 1.1 into the subgroups non-vasoreactivity responders (group 1.1.1) and vasoreactivity responders (group 1.1.2), the reclassification of PH patients with additional features of venous [pulmonary venoocclusive disease (PVOD)] or capillary [pulmonary capillary hemangiomatosis (PCH)] disease into group 1.5, the subdivision of IPAH patients into IPAH patients without comorbidities and IPAH patients with cardiopulmonary comorbidities, and the restructuring of group 5 (20).

PAH associated with congenital shunt lesion is classified into four clinically and prognostically significant groups: Eisenmenger syndrome, correctable or noncorrectable left-to-right shunts, incidental PAH associated with an CHD, and PAH after reparative treatment (*Table 3*).

For everyday clinical practice, the classifications given in the 2022-ESC guideline appear to be sufficient, but in many cases do only limited justice to the complexity of the clinical pictures. A classification according to severity or complexity of CHD does not exist, although complex CHD, in particular univentricular hearts after modified Fontan operation, will become the focus of attention in the future due to their pulmonary vascular involvement (21).

Diagnosis of PAH—general [clinic, laboratory, electrocardiogram (ECG), lung function, spiroergometry, X-ray, magnetic resonance imaging (MRI), computed tomography (CT), ventilation/perfusion (V/Q) scintigraphy]

General

The diagnostic algorithm is used to confirm the diagnosis and clarify PAH, especially to exclude or confirm LHD (group 2 PH) or structural lung disease (group 3 PH).

Clinic

Clinical symptoms are usually attributable to insufficiency of the right ventricle (RV) (22,23). Exertional dyspnea is the most common symptom in adults (24,25).

Laboratory chemical tests

The recommended laboratory chemistry tests at initial diagnosis are given in *Table 4*.

Table 2 Current clinical classification of pulmonary hypertension according to according to 2022 ESC/ERS guidelines (9)

Group	Definition
Group 1: PAH	1.1. Idiopathic PAH
	❖ 1.1.1. Non-responders in the vasoreactivity test
	❖ 1.1.2. Acute responders in the vasoreactivity test
	1.2. Hereditary PAH
	1.3. PAH, associated with drugs/toxins
	1.4.PAH, associated with:
	❖ 1.4.1. Connective tissue disease
	❖ 1.4.2. HIV infection
	❖ 1.4.3. Portal hypertension
	❖ 1.4.4. Congenital heart defect
	❖ 1.4.5. Schistosomiasis
	1.5. PAH with signs of venous/capillary (PVOD/PCH) involvement
	1.6. Persistent PH of the newborn
Group 2: PH, associated with left heart disease	2.1. Heart failure
	❖ 2.1.1. HFpEF
	❖ 2.1.2. HFrEF/HFmrEF
	2.2. Valve disease
	2.3. Congenital/acquired cardiovascular disease associated with post-capillary PH
Group 3: PH, associated with lung disease or hypoxia	3.1. Obstructive lung disease or emphysema
	3.2. Restrictive lung disease
	3.3. Pulmonary disease with mixed restrictive/obstructive pattern
	3.4. Hypoventilation syndrome
	3.5. Hypoxia without lung disease (e.g., high altitude)
	3.6. Pulmonary developmental disorders
Group 4: PH associated with pulmonary arterial obstructions	4.1. Chronic thromboembolic PH
	4.2. Other pulmonary arterial obstructions
Group 5: PH with unclear diseases and/or multifactorial mechanism	5.1. Hematologic diseases
	5.2. Systemic diseases
	5.3. Metabolic diseases
	5.4. Chronic renal insufficiency with or without hemodialysis
	5.5. Pulmonary tumorous thrombotic microangiopathy
	5.6. Fibrosing mediastinitis

ESC/ERS, European Society of Cardiology/European Respiratory Society; PAH, pulmonary arterial hypertension; HIV, human immunodeficiency virus; PVOD, pulmonary venoocclusive disease; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with moderately reduced ejection fraction.

Table 3 Classification of pulmonary hypertension in congenital shunt lesions according to clinical aspects according to 2022 ESC/ERS guidelines (9)

Classification	Clinical aspects
Eisenmenger syndrome	All large intra- and extracardiac defects with initial systemico-pulmonary shunt (left-to-right shunt), in which PVR increases sharply during the course of the disease with resulting bidirectional or pure right-to-left shunt
	Clinically, central cyanosis, secondary erythrocytosis, and cyanosis-related multiorgan damage usually result
PAH associated with predominant systemico-pulmonary shunt, correctable interventrally or surgically or not correctable	Moderate to large defects with predominant low- to moderate-grade systemico-pulmonary blood flow. PVR is mildly to moderately elevated. There is no cyanosis under resting conditions
PAH with small/incidental defects	Markedly increased PVR in the presence of CHD that is not considered hemodynamically significant and is not responsible for the development of increased PVR (usually ventricular septal defects with an echocardiographically measured effective diameter <1 cm or an atrial septal defect <2 cm)
	The clinical picture strongly resembles idiopathic PAH
	Defect closure is contraindicated
PAH after reparative treatment	PAH persisting immediately after repair of CHD or recurring within months or years without existing hemodynamically relevant re/residual shunts

ESC/ERS, European Society of Cardiology/European Respiratory Society; PVR, pulmonary vascular resistance; PAH, pulmonary arterial hypertension; CHD, congenital heart disease.

Table 4 Laboratory chemical and immunological tests for initial diagnosis of pulmonary hypertension according to 2022 ESC/ERS guidelines (9)

Laboratory chemical and immunological studies
Blood count (Hb)
Electrolytes (Na, K)
Kidney function (creatinine, urea, GFR)
Uric acid
Liver assessment (ALT, AST, AP, GGT, bilirubin)
Iron status (serum iron, transferrin, transferrin saturation, ferritin, soluble transferrin receptor)
BNP or NT-proBNP
Hepatitis serology, HIV-tests
Anti-nuclear antibody, anti-centromere antibody, anti-Ro antibody
Markers to exclude antiphospholipid syndrome in CTEPH
Thyroid function (TSH)

ESC/ERS, European Society of Cardiology/European Respiratory Society; Hb, hemoglobin; GFR, glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, acute pancreatitis; GGT, gamma-glutamyl transferase; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone BNP; HIV, human immunodeficiency virus; CTEPH, chronic thromboembolic pulmonary hypertension; TSH, thyroid stimulating hormone.

ECG

A rightward shift of the cardiac electrical axis on ECG has a high predictive diagnostic value for PH (26). However, a normal ECG does not exclude PH.

With a normal ECG in combination with unremarkable cardiac stress markers [B-type natriuretic peptide (BNP)/N-terminal prohormone BNP (NT-proBNP)], there is little likelihood of PH even with increased risk of PH (27,28) (*Table 5*).

Pulmonary function diagnostics and arterial blood gases

Spirometry is normal or only mildly restrictive and/or obstructive altered, higher grade abnormalities are occasionally found in PH-CHD and in group 3 PH (29,30). Lung diffusing capacity for carbon monoxide (DLCO) is normal or mildly reduced (29). Arterial partial pressure of oxygen (PaO_2) is normal or slightly reduced; if severely reduced, right-to-left shunt is suspected, among others. Arterial partial pressure of carbon dioxide ($PaCO_2$) is typically lower than normal due to alveolar hyperventilation and prognostically relevant (31,32). An elevated $PaCO_2$ is highly unusual and reflects alveolar hypoventilation, which per se may be causative or driving PH. Polysomnography is indicated to rule out ventilatory dysfunction (33).

Table 5 ECG changes in patients with according to 2022 ESC/ERS guidelines (9)

Typical ECG changes in PH
P dextroatrial (pulmonale) (P >0.25 mV in lead II, III, aVF)
Extreme right axis deviation or sagittal type (QRS axis >90° or not determinable)
Signs of RV hypertrophy (R/S >1, with R >0.5 mV in V1: R in V1 + S in lead V5 >1 mV)
Right bundle branch block: complete or incomplete, right-sided intraventricular conduction delay (qR or rSR pattern in V1)
RV strain (ST depression/T wave inversion in right precordial leads V1–V4 and inferior leads II, III, aVF)
Prolonged QTc interval (non-specific)

ECG, electrocardiogram; ESC/ERS, European Society of Cardiology/European Respiratory Society; PH, pulmonary hypertension; aVF, arteriovenous fistulae; RV, right ventricle.

Table 6 Radiological signs of PH and accompanying abnormalities according to 2022 ESC/ERS guidelines (9)

Signs of PH and accompanying abnormalities	Signs of left heart disease and pulmonary congestion	Signs of lung disease
Right heart enlargement	Consolidations and milk glass opacities, airbronchograms	Flattening of the diaphragm due to hyperinflation (COPD/emphysema)
Enlargement of the pulmonary artery (incl. aneurysm formation)	Thickening of interlobular septa 'Kerly B' lines	Hypertransparency (COPD/ emphysema)
Rarefaction of the peripheral pulmonary vessels	Pleural effusions	Reduction of lung volume (fibrotic lung disease)
"Water bottles"-shaped cardiac silhouette	Cardiomegaly, increased CTR. Left atrial enlargement (incl. spread carina); left ventricular enlargement	Reticular lactic glaucomatous opacities (fibrotic lung disease)

PH, pulmonary hypertension; ESC/ERS, European Society of Cardiology/European Respiratory Society; COPD, chronic obstructive pulmonary disease; incl., including; CTR, cardiothoracic ratio.

Spiroergometric examination

Spiroergometry shows a typical picture with low end-tidal partial pressure for carbon dioxide ($PETCO_2$), high ventilatory equivalent for carbon dioxide, decreased oxygen pulse [VO_2/heart rate (HR)], and decreased maximal oxygen uptake (peak VO_2) (34).

X-ray thorax

A normal X-ray does not exclude PH (35). Typically, there is enlargement of the right heart and pulmonary artery, with so-called 'pruning' when severe, indicating rarefaction of the peripheral pulmonary arteries (*Table 6*) (22-24,36,37).

Cardiac MRI (cMRI)

RV volume, right ventricular ejection fraction (RVEF) and stroke volume (SV) are considered essential factors for the prognostic assessment of PH using cMRI (15,22,23,38-42).

Non-contrast and contrast-enhanced thoracic CT examinations and digital subtraction angiography

An enlarged PA diameter, a PA to aorta ratio of 0.9, and enlarged RVs are typical findings on CT (35). A PA diameter ≥30 mm, right ventricular outflow tract (RVOT) wall thickness ≥6 mm, and septal deviation ≥140° (or RV:LV ratio ≥1) is highly predictive of PH (43).

The accuracy of contrast CT pulmonary angiography (CTPA) for CTEPH is limited but can be increased using high-quality multidetector CT scanners and interpretation by experienced investigators (44).

V/Q lung scan (scintigraphy)

A V/Q lung scan is recommended to rule out CTEPH (45,46). In the absence of parenchymal lung disease, a normal perfusion scan excludes CTEPH with a negative predictive value of 98% (47,48). Perfusion defects with V/Q mismatch, however, may occur in 7–10% of patients with PVOD/PCH

or PAH (49,50). The presence of contrast in extrapulmonary organs may indicate cardiac or intrapulmonary right-to-left shunt (35).

Abdomen ultrasound

To exclude portal hypertension and in progressive disease with increasing right ventricular dysfunction, an end-organ damage assessment should be performed (51).

Diagnostics of PAH—genetic counseling and testing

Mutations in PAH genes have been identified in familial PAH, IPAH, PVOD/PCH, and anorexigen-associated PAH [*Tab. 13* in the ESC-guideline (52)]. All patients with the above forms of PAH should be informed of the risk of genetic disease and that family members may carry a mutation that increases the risk of PAH, allowing screening and early diagnosis (52,53).

Genetic counseling by appropriately trained PAH specialists (in Germany, for example, with the qualification "Fachgebundene Genetische Beratung") or human geneticists should be performed prior to genetic testing. For asymptomatic family members, this is obligatory in Germany (52).

If the familial mutation is known and an unaffected family member test negative for the mutation, the risk of PAH for that person is the same as for the general population (52).

Tab. 13 in the ESC-guideline (52) summarizes clinical findings that may occur in the context of the above mutations and recommended investigations.

A thorough history and examination is essential, as mild findings may be overlooked.

As more genes associated with PAH are discovered, it becomes more difficult to test them individually. Next-generation sequencing (NGS) has enabled the development of gene panels to examine multiple genes simultaneously (41). However, it is important to verify the genes included in the panel at the time of testing because the composition of gene panels changes as science advances.

Commentary related to ACHDs

It has been shown several times that ACHDs may also have PAH-causing mutations. Therefore, in addition to hereditary PAH, IPAH, PVOD/PCH, and anorexigen-associated PAH, CHD-associated PAH (CHD-APAH) is also listed in the original publication to which the guidelines refer for the explicitly named group of PAH forms with known genetic predisposition (52).

While *Table 7* refers to CHD-APAH only in the gene *SOX17*, notably mutations in the *TBX4* and *BMPR2* genes were also identified in this patient population (54). To date, it is unclear whether mutations may be present in all forms of CHD-APAH.

Especially in patients with simple heart defects [atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), patent foramen ovale (PFO)], a genetic predisposition has been demonstrated so far (55,56).

Initial data from *SOX17* mutation carriers with CHD suggest that, similar to what has been described for *BMPR2* mutation carriers, genetic predisposition may also affect earlier age at diagnosis and associated poorer prognosis in CHD-APAH patients (53).

Particularly noteworthy are chromosome 22q11 deletion syndrome and pulmonary atresia with VSD (PA/VSD) and major aortopulmonary collateral arteries (MAPCAs). The associated PH is very specific and usually does not respond well to targeted PH medication.

Moreover, it is important to recognize that Down syndrome persons with Down syndrome have an increased incidence of PH, often associated with CHD or persistent PH of the newborn (PPHN) and other respiratory comorbidities. The different underlying causes and risk factors for PH require a multidisciplinary treatment approach to these patients.

Although only very few studies address PH-targeted pharmacotherapie in this population, endothelin receptor antagonists (ERA) can improve quality of life, exercise capacity, and functional classification.

Diagnostics of PAH—echocardiography

Among patients with suspected PAH, transthoracic echocardiography (TTE) is used as the most important noninvasive test for assessment of pulmonary vascular hemodynamics and initial estimation of right atrium (RA), RV, and pulmonary trunk pressures in CHD patients. The echocardiographic criteria for PAH assessment listed in the 2022 ESC/ERS guideline on the diagnosis and management of PH must be critically applied in CHD (9). Anatomic-hemodynamic features such as shunts or stenoses in the heart or downstream pulmonary pathway must be taken into account to correctly classify echocardiographically

Table 7 Echocardiographic parameters for PAH assessment and special features in CHD according to 2022 ESC/ERS guidelines (9)

Parameter	Special features for CHD
RV morph and function	Critical application of usual standard values taking into account structural peculiarities of the respective cardiac defect
Systolic gradient across the tricuspid valve (sPAP)	Significance regarding PAH/PH only if tricuspid valve corresponds to subpulmonary AV valve and no post-tricuspid stenosis exists
Early/end-diastolic gradient across pulmonary regurgitation	Limited significance in higher grade pulmonary regurgitation or downstream stenosis
PA width, RVOT acceleration time	PA enlargement in CHD often also independent of PAH/PH
	RVOT acceleration time (norm >105 ms) in complex hemodynamics (e.g., segmental PH, unilateral pulmonary stenosis) insufficiently validated
LV eccentricity index	Not applicable in CHD with residual post-tricuspid shunt (relief of subpulmonary ventricle by right-to-left shunt) or complex anatomy or univentricular circulation

PAH, pulmonary arterial hypertension; CHD, congenital heart disease; ESC/ERS, European Society of Cardiology/European Respiratory Society; RV, right ventricle; sPAP, systolic pulmonary artery pressure; PH, pulmonary hypertension; AV, arteriovenous; PA, pulmonary artery; RVOT, right ventricular outflow tract; LV, left ventricle.

obtained parameters and to identify abnormalities favoring secondary PAH (shunt lesions, etc.).

Echocardiographic PAH assessment in complex anomalies such as CHD with collateral supply to the lung, segmental PAH, or pulmonary vasculopathy with Fontan circulation in a functionally univentricular heart is severely limited.

The following are examples of common echocardiographic parameters used for PAH assessment and specifics for use in CHD.

Diagnosis of PAH—invasive examination (cardiac catheterization and testing)

Important goals of cardiac catheterization examination are:

- Determination of the severity of PH;
- Differentiation of flow-related, pulmonary vascular, and postcapillary components;
- Identification of possible causes of group 3 and 4 PH;
- Identification of patients with heart defects who are still operable.

In general, venous and arterial catheterization should be performed according to a standardized protocol in cases of shunt lesions. In ACHDs >40 years or a risk constellation for coronary artery disease, coronary angiography should be performed in addition. In ACHDs with PAH, a left heart problem may aggravate the PAH. LHD may lead to elevated left atrial pressure, which may be associated with subsequent pulmonary vascular remodelling, vasoconstriction, and an increase in PVR. This has to be determined during invasive diagnostics.

A vasoreactivity test may be helpful in patients with PAH in shunt lesion (ASD, VSD, PDA) with hemodynamically relevant left-to-right shunt and a PVR >3 WU in conjunction with other clinical, laboratory, and imaging findings, to clarify the possibility of defect occlusion (see *Table 8*) (57). However, there are no prospective studies that can reliably predict how PVR in PAH-CHD will develop under treatment in the absence of reactivity in the acute test.

Risk stratification and follow-up

For ACHDs, detailed suggestions for specific risk stratification do not exist in the 2022-ESC guidelines either. The risk stratification using 3- or 4-strata from the guideline cannot be readily adopted for PAH-CHD patients. However, the common parameters are also applied in these patients: WHO functional class, exercise limitation on 6-minute walking distance (6MWD) or ergospirometry, hospitalizations for cardiac events, rhythm profile, pulse oximetry, biomarkers (including NT-proBNP, C-reactive protein, iron metabolism parameters, serum creatinine, serum uric acid, serum albumin, oxygen saturation), and RV function parameters of echocardiography or MRI.

Cardiac catheterization in ACHDs with PAH is complex and not without risk. It is usually not routinely repeated and thus is not a suitable parameter for follow-up observations. Re-catheterization is more likely to occur in cases of

Table 8 Existing and possible additional indicators for assessing reversibility of PAH in congenital heart disease according to van der Feen *et al.* [2019] (57)

Variables for the assessment of reversibility	Effect on/indicative of reversibility	Level of evidence
Age and type of CHD	❖ Younger age at shunt repair favours reversibility	C
	❖ Irreversible PAH is more rapidly induced by high pulmonary flow AND high pulmonary pressure than by high flow only	
	❖ Age below which reversible PAH is likely:	
	◆ TA, AVSD, TGA: <6–12 months	
	◆ VSD, PDA: <1–2 years	
	◆ ASD: 30–40 years	
Comorbidities with increased risk to develop irreversible PAH in CHD	Down syndrome, congenital diaphragmatic hernia, bronchopulmonary dysplasia, arteriovenous malformations, hereditary telangiectasia, hyperthyroidism or rheumatoid arthritis	C
Physical findings indicative of irreversible PAH	Cyanosis at exertion, peripheral oxygen saturation <90%, clubbing, RV-heave, accentuated 2nd pulmonary heart sound, fading of shunt murmur	C
Echocardiography findings indicative of reversible PAH	Net shunt direction is left-to-right	C
	Pulmonary to systemic blood flow ratio	
	(Qp/Qs) is 2:1	

PAH, pulmonary arterial hypertension; CHD, congenital heart disease; TA, tricuspid atresia; AVSD, atrioventricular septal defect; TGA, transposition of the great arteries; VSD, ventricular septal defect; PDA, persistent ductus arteriosus; ASD, atrial septal defect; RV, right ventricle.

diagnostic ambiguity or clinically relevant changes.

Especially for adults with larger shunts or an Eisenmenger reaction, there is a lack of adaptation of the risk criteria or the target criteria for PAH-specific medication, as these patients differ from the other PAH groups in terms of severity, stability, and prognosis of the disease.

Criteria for operability of PAH patients who have not yet developed Eisenmenger syndrome have been defined by various expert panels but are inconsistent. Especially in this patient group, it is difficult to identify predictors that allow or prohibit shunt closure.

The following criteria could serve as therapeutic targets in PAH-CHD: stabilization or improvement in functional class and clinical findings, stable stress test, stable or improved serum BNP levels a stable or improved RV function (on echo or MRI), in individual cases, stable or improved hemodynamics.

The follow-up plan for PAH-CHD is largely consistent with the general recommendations of the ESC/ERS guidelines and includes history, functional class, clinical examination, ECG and long-term ECG, 6-minute walk test, spiroergometry [cardiopulmonary exercise test (CPET)], echocardiography, and laboratory investigations.

Risk stratification and follow-up in special situations (e.g., syndromes, trisomy 21, ...)

Approximately 15% of heart defects are syndromically associated (58). Trisomy 21, the most common chromosomal aberration worldwide with approximately 1 in 800 births (59), is associated with CHDs in approximately 40–50% of cases. Atrioventricular septal defect is the most common, followed by VSD, less commonly isolated ASD of the secondary type, and isolated persistent ductus arteriosus (60,61). In uncorrected shunts, irreversibly fixed PH with shunt reversal may develop early and may lead to significantly shortened survival (62,63). Approximately one-third of all patients with Eisenmenger's reaction have trisomy 21. There is also an increased incidence of PH in individuals with trisomy 21, due to additional genetic, congenital, and environmental factors (64). Even initially, there is an increased risk for the occurrence of PPHN (65) and PH occurring later in life, with an incidence of 1.2–5.2% (65-67), the lifetime prevalence is not known (68). Affected individuals often fall into multiple PH classification categories, which complicates risk stratification and guideline-based therapy (69). An individualized approach, including invasive hemodynamic

evaluation if necessary, by pediatric cardiologists and adult cardiologists with ACHDs certification and expertise in PH is therefore required.

Gender aspects

Although precise prevalence data are not yet available, the female predisposition to PH in CHD is well known (70-72). The exact pathomechanism has not been fully elucidated to date, but a relationship with hormonal balance, is discussed. Currently, sex hormones are thought to lead to a higher prevalence of PAH in women even with shunt lesion (71).

Data from the Dutch CONCOR registry show that women with CHD have a 33% higher risk of developing PAH compared with men (72). In this context, the gender-specific frequency of CHD also plays an important role in the female predominance of PAH. Men tend to have more complex CHD (73,74) and have a higher prevalence of disease with aortic involvement (70,75). In contrast, in women, a higher incidence (male-to-female ratio =0.75) has been observed in recent years (76) of simple shunt defects (ASD, VSD, and atrioventricular septal defect), which in turn are more frequently associated with PAH (77).

Future research is particularly needed regarding gender-specific treatment strategies, taking into account sociocultural sex ("gender") (74,78), as this may also have a relevant impact on manifestation, epidemiology, and pathophysiology (79). Because gender differences are a nonmodifiable risk factor, explicit inclusion in the guideline seems essential.

Conclusions

Comprehensive data and controlled studies on the management of PAH in patients with CHD (PAH-CHD) are limited. Existing studies typically involve a small number of patients with simple shunt lesions that have undergone defect closure, while more complex CHD cases are rarely included. Consequently, it remains uncertain which patients truly benefit from targeted PAH therapies.

Given this gap in research, it is crucial to establish clear recommendations and guidelines for effective patient management and advice on the classification of PAH, diagnostic assessments, genetic counseling, gender considerations, risk stratification, and appropriate follow-up procedures.

Moreover, it is essential to expand specialized care for ACHDs and PAH. This care should be delivered by experts in specialized clinics and practices, in collaboration with patient associations, to ensure that affected individuals receive the necessary attention and support.

Acknowledgments

The first author extends his sincere gratitude for all the invaluable support of research and practice in the field of congenital cardiology, particulary to the Deutsche Herzstiftung e.V., Deutsche Rentenversicherung-Rheinland, Herzkind e.V., the Gesellschaft für Prävention e.V. (GPeV), the Manfred-Roth-Stiftung, and the Dr. Axe-Stiftung. We explicitly thank Dr. Claudia S. Copeland for the professional editing of the final draft of the manuscript.
Funding: This work was funded in part by "Janssen-Cilag GmbH".

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Cardiovascular Diagnosis and Therapy* for the series "Current Management Aspects of Adult Congenital Heart Disease (ACHD): Part VI". The article has undergone external peer review.

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-148/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-148/coif). The series "Current Management Aspects of Adult Congenital Heart Disease (ACHD): Part VI" was commissioned by the editorial office without any funding or sponsorship. H.K. served as the unpaid Guest Editor of the series. H.K. received sponsorship and honoraria from Janssen/Jonson&Johnson, and Bristol Myers Squibb, and participated in the steering board of COMPERA International. G.P.D. has received honoraria and consulting fees from Janssen Pharmaceuticals. I.D. serves as an unpaid board member for Treasurer of the German Society for Pediatric Cardiology and Congenital Heart Disease. S.A. serves as board member for European Society of Cardiology, and Deutsche Herzstiftung. C.A.E. received honoraria for lectures and presentations from OMT and MSD, consulting fees from MSD. C.A.E. is co-inventor of the issued European patent "Gene panel specific for pulmonary hypertension and its uses" (EP3507380). E.G. has received research grants outside the submitted work from Actelion, Janssen, Bayer, MSD, Merck, Ferrer;

research grants to the institution outside the submitted work from Acceleron, Actelion, Bayer, MSD, Janssen, Liquidia, United Therapeutics, OMT; consultancy fees outside the submitted work from Actelion, Janssen, Bayer, MSD, Merck, Ferrer; Speaker honoraria outside the submitted work from Actelion, Bayer/MSD, GSK, AOP, Janssen, phev, OMT, GEBRO, Ferrer, GWT; participation in AdBoards from MSD and Ferrer; unpaid board member for A DUE Steering committee and patient organisation phev. M.H. received consulting fees, honoraria, and travel support from Janssen. S.M. received Research Grant from German Center for Lung Research (DZL). A.U. received consulting fees from Medtronic. U.H. serves as an unpaid board member for Deutsche Gesellschaft für Kinderkardiologie und Angeborene Herzfehler, and Deutsche Gesellschaft für Kinder- und Jugendmedizin. C.A. received lecture and consulting fees from Janssen. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Hoffman JIe. The global burden of congenital heart disease. Cardiovasc J Afr 2013;24:141-5.
2. Deutsche Herzstiftung e.V. Deutscher Herzbericht 2021. Available online: https://herzstiftung.de/system/files/2022-09/DHB21-Herzbericht-2021.pdf
3. Mandalenakis Z, Giang KW, Eriksson P, et al. Survival in Children With Congenital Heart Disease: Have We Reached a Peak at 97%? J Am Heart Assoc 2020;9:e017704.
4. Henning RJ. Diagnosis and treatment of adults with congenital heart disease. Future Cardiol 2020;16:317-42.
5. Neidenbach R, Niwa K, Oto O, et al. Improving medical care and prevention in adults with congenital heart disease-reflections on a global problem-part II: infective endocarditis, pulmonary hypertension, pulmonary arterial hypertension and aortopathy. Cardiovasc Diagn Ther 2018;8:716-24.
6. Rosenkranz S, Delcroix M, Giannakoulas G, et al. The 'Ten Commandments' of the 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2023;44:792-3.
7. Rosenkranz S. 2022 ESC/ERS guidelines on the diagnostics and treatment of pulmonary hypertension: A focussed review. Herz 2023;48:23-30.
8. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Kardiol Pol 2015;73:1127-206.
9. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618-731.
10. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2023;61:2200879.
11. Kovacs G, Olschewski A, Berghold A, et al. Pulmonary vascular resistances during exercise in normal subjects: a systematic review. Eur Respir J 2012;39:319-28.
12. Wolsk E, Bakkestrøm R, Thomsen JH, et al. The Influence of Age on Hemodynamic Parameters During Rest and Exercise in Healthy Individuals. JACC Heart Fail 2017;5:337-46.
13. Maron BA, Brittain EL, Hess E, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. Lancet Respir Med 2020;8:873-84.
14. Xanthouli P, Jordan S, Milde N, et al. Haemodynamic phenotypes and survival in patients with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension. Ann Rheum Dis 2020;79:370-8.
15. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. Lancet Respir Med 2016;4:306-22.
16. van Riel AC, Schuuring MJ, van Hessen ID, et al. Contemporary prevalence of pulmonary arterial hypertension in adult congenital heart disease following the updated clinical classification. Int J Cardiol 2014;174:299-305.
17. Lammers AE, Bauer LJ, Diller GP, et al. Pulmonary hypertension after shunt closure in patients with simple congenital heart defects. Int J Cardiol 2020;308:28-32.
18. Kaemmerer AS, Gorenflo M, Huscher D, et al. Medical

treatment of pulmonary hypertension in adults with congenital heart disease: updated and extended results from the International COMPERA-CHD Registry. Cardiovasc Diagn Ther 2021;11:1255-68.
19. Neidenbach RC, Lummert E, Vigl M, et al. Non-cardiac comorbidities in adults with inherited and congenital heart disease: report from a single center experience of more than 800 consecutive patients. Cardiovasc Diagn Ther 2018;8:423-31.
20. Heberling M, Grünig E, Kolditz M, et al. Pulmonale Hypertonie – alte vs. neue Leitlinie Hämodynamische Definition und klinische Klassifikation – Was ändert sich 2022? Aktuelle Kardiologie 2023;12:16-21.
21. Kaemmerer H, Apitz C, Brockmeier K, et al. Pulmonary hypertension in adults with congenital heart disease: Updated recommendations from the Cologne Consensus Conference 2018. Int J Cardiol 2018;272S:79-88.
22. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75.
23. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
24. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107:216-23.
25. Jing ZC, Xu XQ, Han ZY, et al. Registry and survival study in chinese patients with idiopathic and familial pulmonary arterial hypertension. Chest 2007;132:373-9.
26. Kovacs G, Avian A, Foris V, et al. Use of ECG and Other Simple Non-Invasive Tools to Assess Pulmonary Hypertension. PLoS One 2016;11:e0168706.
27. Bonderman D, Wexberg P, Martischnig AM, et al. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. Eur Respir J 2011;37:1096-103.
28. Klok FA, Surie S, Kempf T, et al. A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Thromb Res 2011;128:21-6.
29. Sun XG, Hansen JE, Oudiz RJ, et al. Pulmonary function in primary pulmonary hypertension. J Am Coll Cardiol 2003;41:1028-35.
30. Meyer FJ, Ewert R, Hoeper MM, et al. Peripheral airway obstruction in primary pulmonary hypertension. Thorax 2002;57:473-6.
31. Mélot C, Naeije R. Pulmonary vascular diseases. Compr Physiol 2011;1:593-619.
32. Harbaum L, Fuge J, Kamp JC, et al. Blood carbon dioxide tension and risk in pulmonary arterial hypertension. Int J Cardiol 2020;318:131-7.
33. Jilwan FN, Escourrou P, Garcia G, et al. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. Chest 2013;143:47-55.
34. Sun XG, Hansen JE, Oudiz RJ, et al. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 2001;104:429-35.
35. Remy-Jardin M, Ryerson CJ, Schiebler ML, et al. Imaging of pulmonary hypertension in adults: a position paper from the Fleischner Society. Eur Respir J 2021;57:2004455.
36. Ascha M, Renapurkar RD, Tonelli AR. A review of imaging modalities in pulmonary hypertension. Ann Thorac Med 2017;12:61-73.
37. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42-50.
38. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
39. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561-632.
40. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates from a systematic literature review. Pulm Circ 2021;11:2045894020977300.
41. Montani D, Girerd B, Jaïs X, et al. Screening for pulmonary arterial hypertension in adults carrying a BMPR2 mutation. Eur Respir J 2021;58:2004229.
42. Certain MC, Chaumais MC, Jaïs X, et al. Characteristics and Long-term Outcomes of Pulmonary Venoocclusive Disease Induced by Mitomycin C. Chest 2021;159:1197-207.
43. Swift AJ, Dwivedi K, Johns C, et al. Diagnostic accuracy

of CT pulmonary angiography in suspected pulmonary hypertension. Eur Radiol 2020;30:4918-29.
44. Dong C, Zhou M, Liu D, et al. Diagnostic accuracy of computed tomography for chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. PLoS One 2015;10:e0126985.
45. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J 2019;53:1801915.
46. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41:543-603.
47. He J, Fang W, Lv B, et al. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. Nucl Med Commun 2012;33:459-63.
48. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007;48:680-4.
49. Giordano J, Khung S, Duhamel A, et al. Lung perfusion characteristics in pulmonary arterial hypertension (PAH) and peripheral forms of chronic thromboembolic pulmonary hypertension (pCTEPH): Dual-energy CT experience in 31 patients. Eur Radiol 2017;27:1631-9.
50. Seferian A, Helal B, Jaïs X, et al. Ventilation/perfusion lung scan in pulmonary veno-occlusive disease. Eur Respir J 2012;40:75-83.
51. Rosenkranz S, Howard LS, Gomberg-Maitland M, et al. Systemic Consequences of Pulmonary Hypertension and Right-Sided Heart Failure. Circulation 2020;141:678-93.
52. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. Eur Respir J 2019;53:1801899.
53. Gräf S, Haimel M, Bleda M, et al. Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. Nat Commun 2018;9:1416.
54. Eichstaedt CA, Belge C, Chung WK, et al. Genetic counselling and testing in pulmonary arterial hypertension: a consensus statement on behalf of the International Consortium for Genetic Studies in PAH. Eur Respir J 2023;61:2201471.
55. Zhu N, Swietlik EM, Welch CL, et al. Rare variant analysis of 4241 pulmonary arterial hypertension cases from an international consortium implicates FBLN2, PDGFD, and rare de novo variants in PAH. Genome Med 2021;13:80. Erratum in: Genome Med 2021;13:106.
56. Montani D, Lechartier B, Girerd B, et al. An emerging phenotype of pulmonary arterial hypertension patients carrying SOX17 variants. Eur Respir J 2022;60:2200656.
57. van der Feen DE, Bartelds B, de Boer RA, et al. Assessment of reversibility in pulmonary arterial hypertension and congenital heart disease. Heart 2019;105:276-82.
58. Hartman RJ, Rasmussen SA, Botto LD, et al. The contribution of chromosomal abnormalities to congenital heart defects: a population-based study. Pediatr Cardiol 2011;32:1147-57.
59. Bull MJ. Down Syndrome. N Engl J Med 2020;382:2344-52.
60. Jensen KM, Bulova PD. Managing the care of adults with Down's syndrome. BMJ 2014;349:g5596.
61. Morris JK, Garne E, Wellesley D, et al. Major congenital anomalies in babies born with Down syndrome: a EUROCAT population-based registry study. Am J Med Genet A 2014;164A:2979-86.
62. Bush D, Galambos C, Ivy DD, et al. Clinical Characteristics and Risk Factors for Developing Pulmonary Hypertension in Children with Down Syndrome. J Pediatr 2018;202:212-219.e2.
63. Körten MA, Helm PC, Abdul-Khaliq H, et al. Eisenmenger syndrome and long-term survival in patients with Down syndrome and congenital heart disease. Heart 2016;102:1552-7.
64. Naumburg E, Söderström L, Huber D, et al. Risk factors for pulmonary arterial hypertension in children and young adults. Pediatr Pulmonol 2017;52:636-41.
65. Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 2010;121:20-5.
66. Hawkins A, Langton-Hewer S, Henderson J, et al. Management of pulmonary hypertension in Down syndrome. Eur J Pediatr 2011;170:915-21.
67. Weijerman ME, van Furth AM, van der Mooren MD, et al. Prevalence of congenital heart defects and persistent pulmonary hypertension of the neonate with Down syndrome. Eur J Pediatr 2010;169:1195-9.
68. Rosenzweig EB, Abman SH, Adatia I, et al. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J 2019;53:1801916.

69. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation 2015;132:2037-99.
70. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. Gender and outcome in adult congenital heart disease. Circulation 2008;118:26-32.
71. Warnes CA. Sex differences in congenital heart disease: should a woman be more like a man? Circulation 2008;118:3-5.
72. Shapiro S, Traiger GL, Turner M, et al. Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Chest 2012;141:363-73.
73. Yoo BW. Epidemiology of Congenital Heart Disease with Emphasis on Sex-Related Aspects. Adv Exp Med Biol 2018;1065:49-59.
74. Freilinger S, Andonian C, Beckmann J, et al. Differences in the experiences and perceptions of men and women with congenital heart defects: A call for gender-sensitive, specialized, and integrative care. International Journal of Cardiology 2021;4:100185.
75. Marelli AJ, Mackie AS, Ionescu-Ittu R, et al. Congenital heart disease in the general population: changing prevalence and age distribution. Circulation 2007;115:163-72.
76. Lindinger A, Schwedler G, Hense HW. Prevalence of congenital heart defects in newborns in Germany: Results of the first registration year of the PAN Study (July 2006 to June 2007). Klin Padiatr 2010;222:321-6.
77. Sarikouch S, Boethig D, Beerbaum P. Gender-specific algorithms recommended for patients with congenital heart defects: review of the literature. Thorac Cardiovasc Surg 2013;61:79-84.
78. Mair KM, Johansen AK, Wright AF, et al. Pulmonary arterial hypertension: basis of sex differences in incidence and treatment response. Br J Pharmacol 2014;171:567-79.
79. Regitz-Zagrosek V. Sex and gender differences in health. Science & Society Series on Sex and Science. EMBO Rep 2012;13:596-603.

Cite this article as: Kaemmerer H, Diller GP, Dähnert I, Achenbach S, Eichstaedt CA, Eicken A, Freiberger A, Freilinger S, Geiger R, Gorenflo M, Grünig E, Hager A, Huntgeburth M, Kaemmerer-Suleiman AS, Kozlik-Feldmann R, Lammers AE, Nagdyman N, Michel S, Schmidt KH, Suleiman M, Uebing A, von Scheidt F, Herberg U, Apitz C. Pulmonary hypertension in adults with congenital heart defects (ACHDs)—in light of the 2022 ESC PAH guidelines—part I: definition, epidemiology, classification, diagnostics, genetics, risk stratification and follow-up, gender aspects. Cardiovasc Diagn Ther 2024;14(5):935-948. doi: 10.21037/cdt-24-148