Review Article

Pulmonary hypertension in adults with congenital heart defects (ACHDs) in light of the 2022 ESC PAH guidelines—part II: supportive therapy, special situations (pregnancy, contraception, non-cardiac surgery), targeted pharmacotherapy, organ transplantation, special management (shunt lesion, left ventricular disease, univentricular hearts), interventions, intensive care, ACHD follow-up, future perspective

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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

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infrequently persists, redevelops in older age, and is associated with significant morbidity and mortality. 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. After the first part commenting on a broad range of topics like definition, epidemiology, classification, diagnostics, genetics, risk stratification and follow-up, and gender aspects, the second part focuses on supportive therapy, special situations (pregnancy, contraception, non-cardiac surgery), targeted pharmacotherapy, organ transplantation, special management [shunt lesion, left ventricular (LV) disease, univentricular hearts], interventions, intensive care, ACHD follow-up, and future perspective. In the present article, therefore, this topic is commented on from the perspective of congenital cardiology. 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 defect (CHD); Eisenmenger syndrome (ES)

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Introduction

The European Society of Cardiology (ESC) guidelines provide general lifestyle recommendations for pulmonary hypertension (PH), particularly with regard to pregnancy, immunization (influenza and pneumococcal), physical activity and exercise, behavior on flights, recommendations on elective surgery, and psychological care and linkage to self-help organizations.

According to the ESC/European Respiratory Society (ERS) guidelines, PH patients should be encouraged to be active within symptom limits, as recent studies have shown the beneficial impact of exercise training on exercise capacity and quality of life (1-6).

Only cursory comments are made on congenital heart defect (CHD) in this regard in the recommendations.

Recommendations for vaccine prophylaxis in CHD are similar to those seen in other forms of PH.

Left unconsidered is endocarditis prophylaxis, which plays an important role in adults with CHD (ACHDs), especially in cyanotic patients.

However, physical stress and exercise in CHD should be controlled by physicians with sufficient experience in ACHD, especially since the influence of exercise on prognosis has not been clarified.

Pregnancy and contraception, as well as health-conscious behavior while traveling, are commented on elsewhere.

Management recommendations and therapy for pulmonary arterial hypertension (PAH) in CHD

Air travel, stay at altitude

Air travel and (recreational) stays at altitude are also relevant for PAH patients. Even in healthy individuals, a stay at altitudes above 1,500 to 2,000 m above sea level (a.s.l.) (hypobaric hypoxia) leads to pulmonary vasoconstriction with an individually variable increase in pulmonary arterial pressure. Compensatory increases in respiratory minute volume and cardiac output (CO) are observed (7,8). In patients with PAH, hypoxia may be more pronounced and cause increased pulmonary vasoconstriction, which leads to an increase in pulmonary pressure and resistance, depending on the individual patient.

Air travel is comparable to a stay at altitude. During air travel, an altitude equivalent of a maximum of 2,438 m (8,000 ft) a.s.l. is achieved by adjusting the cabin pressure; this corresponds to a reduced oxygen partial pressure of 60–75 mmHg and an oxygen content of 15.1% at sea level (7).

With limited data, previous studies indicate that time-limited air travel and high-altitude stays (less than 1 day) are well tolerated by patients with clinically stable PAH (9). Symptoms during air travel are associated with the length of the trip, preexisting oxygen therapy, and physical exertion or stress during check-in or transfer.

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Despite limited validity, the ESC guidelines use measurement of resting oxygen saturation in normoxia as an indicator for oxygen administration during air travel. In-flight oxygen administration is recommended in patients already receiving oxygen at sea level and in patients with a partial pressure of arterial oxygen (PaO_2) <8 kPa (60 mmHg) or oxygen saturation <92%. In patients who do not normally receive oxygen, a flow rate of 2 L/min is recommended, whereas patients on long-term oxygen therapy should increase the flow rate during flight (usually doubled flow rate).

For Eisenmenger syndrome (ES) and other CHDs with PAH, the ESC guidelines do not provide further recommendations. In stable condition, air travel is well tolerated by Eisenmenger patients despite marked cyanosis during flight, but dehydration should be avoided to prevent paradoxical emboli and anticoagulation should be discussed (8).

The ESC guidelines recommend carrying written information about the disease, medication lists, and medication in sufficient quantity to increase the safety of PAH patients. PAH-CHD patients should be aware of specialty centers near their destination.

Supportive therapy, therapy algorithm [includes heart failure (diuretics, glycosides, vasodilators), anticoagulation, O_2 therapy, erythrocytosis, iron deficiency]

In addition to the general measures, the ESC guidelines describe a so-called supportive therapy, which includes the use of diuretics, oxygen, and oral anticoagulants.

In general, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-2 receptor antagonists, beta-blockers, and ivabradine are not recommended in PAH, except in the presence of comorbidities (such as arterial hypertension, coronary artery disease, or left heart failure) and should be used with caution as they might affect systemic vascular resistance and lower blood pressure without proven beneficial effect. Iron deficiency or anemia may also be considered in PAH patients.

O_2 treatment should be considered if it leads to an increase in arterial oxygen saturation and relieves symptoms.

On CHD, we find the complementary note that oral anticoagulation may be considered in pulmonary arterial thrombosis or heart failure in the absence of significant hemoptysis. In symptomatic hyperviscosity, phlebotomy with isovolemic replacement may be considered if the hematocrit (Hct) is >65%, and additional iron treatment may be considered if plasma ferritin levels are low.

These recommendations require some additions.

Heart failure therapy (diuretics, vasodilators, digoxin) should be considered, especially in CHD with significant Li-Re shunt and signs of left ventricular (LV) strain potentially contributing to the development/progression of PH/PAH. Perhaps also SGLT2 inhibitor is a promising option in this setting (10).

Diuretics are used in decompensated right heart failure with fluid retention. In right-to-left shunt and especially in Eisenmenger's syndrome, metabolically neutral loop diuretics are preferred. When administered orally, torasemide appears superior to furosemide. Low-dose hydrochlorothiazide can be added to prevent loop diuretic resistance. The additional administration of aldosterone antagonists should also be considered.

Excessive reduction of intravascular volume should be avoided because of the risk of consecutive prerenal renal failure. In cyanotic patients with erythrocytosis, diuretic administration can lead to hemoconcentration with Hct increase, which affects the rheological properties of the blood.

Cyanotic patients with ES paradoxically show an increased risk of bleeding on the one hand and an increased risk of thrombosis on the other hand due to changes in platelet function, platelet count, and coagulation cascade (11-19).

Oral anticoagulation may be necessary in patients without significant hemoptysis in central or peripheral thromboembolism or pulmonary arterial thrombosis if concomitant complications exist, such as atrial arrhythmias or artificial valves/conduits. However, there are no valid data to date that oral anticoagulation favorably affects morbidity and mortality in Eisenmenger patients.

Under oral anticoagulation, Eisenmenger patients must be monitored particularly carefully. The determination of coagulation parameters is complicated and requires special knowledge. For the determination of the coagulation parameters, the amount of sodium citrate in determination tubes must always be adjusted to the current Hct (17).

There are only isolated reports on the use of direct oral anticoagulants (20).

Supplemental O_2 therapy is controversial in PH/PAH-CHD or ES. It can be given, taking into account potential risks and side effects (such as dry nasal mucosa, nosebleeds, sleep disturbances, etc.), if it shows a constant increase in arterial O_2 saturation underneath and patients become less symptomatic (20).

Significant in ES is secondary erythropoietin-mediated erythrocytosis as a physiological adaptation to chronic hypoxemia. The lower the oxygen saturation, the higher the

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erythrocyte count and Hct, at least in patients without iron deficiency. For Eisenmenger patients, depending on oxygen saturation, only hemoglobin values above 18 g/dL are adequate. Prophylactic or routine phlebotomies to lower Hct are not warranted.

Phlebotomy is indicated only for temporary relief of clinically relevant hyperviscosity symptoms in symptomatic secondary erythrocytosis if volume deficiency (exsiccosis) or iron deficiency has been previously excluded. When performing phlebotomy, adequate volume replacement must be ensured.

Relative iron deficiency anemia is often misdiagnosed in cyanotic patients and concomitant iron deficiency is overlooked. Complete screening (including ferritin, transferrin, soluble transferrin receptor, transferrin saturation) is required for detection of iron deficiency, as determination of peripheral red cell parameters [mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCV concentration (MCHC)] alone is insufficient (21). When compensating for iron deficiency, it should be noted that even low-dose iron supplementation can lead to an excessive increase in HKT and hyperviscosity (22). A later study in cyanotic ACHD has shown favorable results with intravenous iron substitution regarding rebound erythrocytosis and hyperviscosity (23). Chronic hemolytic anemia as it may be present in shunt lesions or dysfunctional prosthetic valves can contribute to certain types of PH (9).

Vasodilating drugs [e.g., Ca antagonists, ACE inhibitors, angiotensin receptor blockers (ARBs)] can lead to cyanosis deepening and threatening deterioration of hemodynamics in right-to-left shunts.

Detailed discussion of ES can be found in the special literature (12-15,17,18,24).

Pregnancy and contraception

In patients with CHD, the special features of a frequently present shunt lesion must be taken into account. Since the clinical course depends on the extent of pulmonary resistance increase and, if applicable, on shunt conditions, the consideration of the patient with PAH in CHD must be highly individualized.

The recommendations for patients with ES are also clear in the current guidelines and pregnancy is clearly discouraged. Most deaths in these patients occur during delivery or in the first weeks after birth (13,25).

At least in Eisenmenger patients, termination of pregnancy should be sought as early as possible if pregnancy has occurred.

In CHD with PAH, many women are on targeted PAH therapy. This can be done in pregnancy with phosphodiesterase-5 inhibitors (PDE5is), inhaled/intravenous/subcutaneous prostaglandin analogues, or in responders with calcium blockers (26,27). There is concern about their use in patients with open shunts and ES. Combination therapies with parenteral or inhaled prostanoids are possible. Intravenous epoprostenol is advised for patients in World Health Organization (WHO) functional class (FC) III/IV or with severe right heart problems (28).

Due to the high maternal risk during delivery and postpartum, it is recommended to be connected to a tertiary care center, if necessary with the option of extracorporeal membrane oxygenation (ECMO) therapy.

A more neutral stance can be taken toward patients with mild PAH. However, since the course of the disease is hardly calculable even in the case of mild or moderate PAH, and clinical deterioration of the cardiac situation may still occur during or even weeks after pregnancy, education plays a major role.

Contraceptive counseling is necessary in all patients with CHD and PAH, especially with reference to consequences of inadequate contraception. It is important to note that the endothelin blocker bosentan decreases the efficacy of orally administered progestins by enzyme reduction, and therefore safe contraception cannot be ensured. This is not the case for macitentan.

The care of patients with PAH in CHD is very challenging and benefits from patient management in expert centers, in cooperation with a Pregnancy Heart Team, and from simultaneous psychological support for patients and their families. Although targeted therapies have made pregnancy safer for patients with PH, the risk of death remains high. Therefore, the recommendation should be clear to avoid pregnancy.

Surgical procedures (non-cardiac)

Patients with CHD and PH, esp, cyanotic patients with Eisenmenger physiology, have a high risk of complications and mortality even during noncardiac interventions (29-31). According to the literature, perioperative non-cardiac/non-obstetric mortality is around 2% in elective procedures and as high as 15% in emergency procedures (32).

Severity of PH, type of underlying CHD, presence of shunt between pulmonary and systemic circulation, ventricular function, and type and duration of procedure to

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be performed determine individual patient risk.

The risk of complications results primarily from an (acute) increase in pulmonary vascular resistance (PVR) (pulmonary hypertensive crises), right heart failure with inadequate cardiac ejection, inadequate coronary or organ perfusion, and cardiac arrhythmias (33).

With preexisting (shunt) connection between pulmonary and systemic circulation, cardiac ejection is often preserved, but right-to-left shunt with pulmonary resistance increase can lead to fulminant hypoxemia, which is exacerbated by increased intrathoracic pressure during ventilation or by systemic vasodilation during anesthesia (33). Preexisting impaired venous function increases perioperative risk (33).

Critical to the perioperative management of patients with CHD and PAH is the preoperative benefit-risk assessment by a multidisciplinary team (34). the cardiac history, indication, urgency and benefit of the procedure, severity of PH, and, of course, the patient's level of suffering and desire must be considered. However, emergency surgery must not be delayed by this.

Intraoperative patient management requires anesthesiologists, cardiologists, and surgeons to have a deep pathophysiological understanding of the effects of anesthesia and surgery on hemodynamics, as well as experience with modern targeted pharmacotherapy of PH.

Preoperative optimization of hemodynamics, oxygenation, volume status, and standard medical therapy helps to reduce perioperative complications in CHD with PAH. Especially in cyanotic CHD, preoperative endocarditis prophylaxis is required in many cases (33).

In addition to close postoperative monitoring with CO_2 control to avoid hypoxia- or hypercapnia-triggered pulmonary hypertensive crises, adequate perioperative pain control is important to avoid stress reactions with metabolic derailment and to allow early mobilization.

Patients with CHD and PAH should preferably be treated in specialized centers where congenital cardiologists, anesthesiologists, and surgeons cooperate and the appropriate care environment is provided (35,36).

Targeted pharmacotherapy

Therapeutic outcomes in ACHD and PAH have improved with the availability of new PAH therapies, advances in surgical and perioperative treatment, and more recently a team-based, multidisciplinary approach in specialized PH centers.

Compared with other PAH subgroups (group 1), there are limited data on the use of targeted PAH pharmacotherapy in ACHD.

The guidelines focus on two particular PAH groups in ACHD. These are ES and PAH patients with simple heart defects and after defect occlusion.

Bosentan is considered to improve exercise capacity as well as PVR in patients with ES in New York Heart Association (NYHA)/WHO FC III (37). A more recent randomized, blinded, placebo-controlled trial examining the efficacy of macitentan in Eisenmenger's patients found no definite evidence of an effect of macitentan on 6-minute walk distance in a mixed cohort of patients with Eisenmenger's syndrome (6-minute walk distance improved in both the treatment and placebo arms), but did in the macitentan study arm, where there was a decrease in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and PVR (38).

Experience with other endothelin receptor antagonists (ERAs) and PDE5is has shown favorable functional and hemodynamic outcomes in ES.

A monocentric pilot study in which nebulized iloprost was given in addition to oral PAH therapy failed to provide evidence of further improvement in 6-minute walking distance in ES (39).

In principle, a sequential and symptom-oriented treatment strategy is recommended for patients with persistent symptoms or those Eisenmenger patients who clinically worsen during the course. This should start with oral ERA (or PDE5i) treatment and be escalated over the course. If symptoms do not improve sufficiently with oral therapies, parenteral options should be proactively considered.

Because there is a theoretical risk of paradoxical embolism for intravenous therapy via a central venous catheter in right-to-left shunt vitiated patients, subcutaneous prostacyclin analog application should be considered, although it is also not free of side effects.

Unchanged from previous PAH guidelines, overall evidence of symptomatic improvement in Eisenmenger's patients in NYHA/WHO FC III with PAH drug therapy continues to exist. This is true both in the short term under controlled study conditions and in the medium to long term under "real-world" conditions.

For patients in NYHA/WHO FC II, formal evidence still does not exist; however, in clinical practice, accurate assignment to WHO FCs is problematic because of often fluctuating symptoms.

Limited data are available on combination therapy for ES. Current guidelines support proactive sequential combination therapy. This is in line with expert opinion and lived practice

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at major centers. However, it remains to be noted that the evidence base for this recommendation is limited and mostly considered individually based on the clinical course.

A randomized controlled trial (RCT) on the potential benefit of dual therapy with sildenafil in addition to bosentan in ES failed to show significant symptomatic or functional improvement. However, these were stable patients with no clear indication for therapy escalation (40). In contrast, the results of nonrandomized prospective studies (albeit with limited case numbers and methodological limitations) support this practice [e.g., (41)].

For the treatment of PAH, sotatercept has recently emerged as a promising therapeutic agent with a novel mechanism of action that restores the balance between antiproliferative and proproliferative signals in favor of apoptotic and antiproliferative effects.

A phase 2 randomized, placebo-controlled, double-blind study (PULSAR) demonstrated the efficacy of sotatercept compared with placebo in PAH patients, including those with corrected congenital shunts (42). This data is consistent with results of major phase III trials for macitentan (SERAPHIN trial) and selexipag (GRIPHON trial) (43,44).

In another randomized, double-blind, placebo-controlled, multicenter, parallel-group phase 3 study (STELLAR), 16 of 323 PAH patients enrolled had corrected CHD. There was an improvement in exercise capacity and NT-proBNP levels and a significant improvement in time to death or non-fatal clinical worsening in the sotatercept group versus placebo (45).

The phase 3 randomized, placebo-controlled, double-blind study (ZENITH) is evaluating the occurrence of a first morbidity or mortality event in PAH patients, including those with simple corrected congenital shunts, receiving sotatercept in addition to maximal standard therapy (46).

Subcutaneous or intravenous therapy should be reserved for selected patients with advanced, refractory symptoms on oral combination therapy. Potential side effects (paradoxical embolism, apoplectic insults, septic complications) should be considered. Data on inhaled prostanoid therapy for Eisenmenger's syndrome currently remain limited and therapy is limited by the short half-life of the substance with short application intervals.

It is considered certain that patients with PAH have increased mortality after defect correction compared with patients with ES. These patients have been included in recent RCTs of PAH therapies and should be evaluated based on a comprehensive risk assessment.

Unlike other forms of PAH in CHD, robust evidence exists for symptomatic and prognostic improvement in patients with PAH after defect correction of simple isolated defects [atrial septal defect (ASD), ventricular septal defect (VSD), or persistent ductus arteriosus (PDA)]. Two recent studies have demonstrated a corresponding morbi-mortality benefit for macitentan and selexipag (43,44). Accordingly, these patients should be treated proactively according to the general PAH recommendations.

The effect of PAH therapies in patients with existing systemic pulmonary shunts (without ES) is less well established. Patients with small/incidental cardiac defects ("co-incidental PAH") should be treated with PAH drugs analogously to idiopathic PAH (IPAH) patients.

The efficacy of PAH therapies in patients with segmental PH remains controversial. While some series have reported promising results, there have been cases in which therapies have not been tolerated.

Patients with small/incidental cardiac defects should be assumed to have IPAH with incidental presence of a cardiac defect (not relevant from the PAH point of view). Thus, these patients should be treated as IPAH patients.

In individual cases, differentiation between co-incidental PAH and CHD-associated PAH can be difficult. In this case, invasive data as well as cardiac magnetic resonance imaging (cMRI) examinations (shunt conditions) and individual case discussions with appropriate experts are particularly helpful. Especially in the case of existing systemic-pulmonary shunts (without ES) and PVR increase, a differentiated individual case decision after invasive clarification with consultation of experts is essential. This includes the decision on possible shunt closure as well as decisions on drug treatment (especially in case of a planned "treat-and-repair" strategy).

The treatment decision in segmental PAH remains a case-by-case decision.

Lung transplantation (LTx) and heart-LTx (HLTx)

Indication for LTx and HLTx in PH-CHD

Failure of medical therapy is an indication for evaluation or listing for LTx in patients with PH under the following conditions.

Evaluation for LTx should be performed if there is an intermediate to high risk of death within 1 year, i.e., functional WHO FC III, 165–319 m on 6-minute walk test and NT-proBNP 650–1,100 ng/L despite adequate oral combination therapy.

Listing for LTx should be performed if there is a high risk of death within 1 year, i.e., functional WHO FC IV, <165 m on the 6-minute walk test, and NT-proBNP

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>1,100 ng/L despite optimized drug therapy including subcutaneous or intravenous prostacyclin analogues.

In PH due to CHDs, the basic option is combined HLTx or double LTx (DLTx) in combination with lesion correction.

The indication for combined HLTx should be limited to Eisenmenger patients with complex CHDs (47,48).

In diseases with pulmonary venous occlusion disease (PVOD), evaluation for LTx is recommended at diagnosis because drug therapy is not very effective.

It is possible to obtain an exceptional lung allocation score if certain criteria are met: cardiac index <2 L/m^2, central venous pressure >15 mmHg, or bilirubin elevation by 50% of normal or creatinine elevation by >50% of normal (49).

Bridging until transplantation

If medical therapy is not sufficient, the following invasive measures are available to prevent right heart failure: balloon atrioseptostomy (BAS), reversed Potts shunt (50), veno-arterial extracorporeal life support (ECLS), and the paracorporeal lung assist device [pulmonary artery-left atrium (PA-LA) shunt with oxygenator] (51).

Results after LTx/HLTx

Looking at data currently published in the ISHLT registry for the most recent era (2002 onward), the median survival for patients who survived the first year was 9.4 years for LTx and 12.8 years for HLTx. One-year survival for LTx and HLTx is 85% and 70%, respectively (47).

Special situations of PH in ACHD

Management of shunt lesion (recommendations for closure of a left-to-right shunt in PH-CHD)

Catheter interventional therapy

Before closure of a shunt lesion and suspicion of PAH, a hemodynamic examination must be performed, if necessary with responsiveness testing of the pulmonary vascular bed, to determine whether pre- or post-capillary PAH is present (52,53). The hemodynamic examination of a CHD-PAH patient requires detailed knowledge of the physiology and anatomy of CHD and should therefore be performed in a specialized center.

cMRI can be an important adjunct to invasive hemodynamic diagnosis in difficult decision making with borderline hemodynamics. Flow values from cMRI can be used to calculate PVR.

The decision whether a defect can be closed depends largely on the shunt volume and PVR.

Closure of pretricuspid defects (defects in the atrial septum)

The indication for defect closure is made according to the same principles for all anatomic types of ASD. If technically feasible and indicated, catheter interventional closure is the therapy of choice (54-56).

If LV end-diastolic pressure (LVEDP) is elevated (>12 mmHg), a balloon test should be performed to rule out significant LV diastolic dysfunction (57). An increase in left atrial pressure or LVEDP to >20 mmHg or an increase >10 mmHg is considered a risk factor for LV diastolic dysfunction with the risk of pulmonary edema after ASD occlusion (57,58).

In patients with LV disease, consider partial ASD closure (59,60). Meanwhile, catheter interventional treatment of patients with superior sinus venosus defect using covered stents is also possible (61,62) (*Table 1*).

Closure of post-tricuspid defects (VSD, PDA)

The indication for VSD closure according to the current ESC recommendations is summarized in *Table 1*.

Interventional closure is possible with self-centering nitinol occluders, coils, and even conical duct occluders if the anatomy of the defect allows implantation of the occluder without compromising adjacent cardiac structures (63-67).

The indication for PDA closure in patients with PAH follows the recommendations for VSD closure.

With a PVR <3 Wood units (WU) and signs of LV volume loading, closure is recommended. If there is significant left-to-right shunt and a PVR between 3 and 5 WU, PDA closure should also be considered. A large, nonpressure-separating PDA is a diagnostic and therapeutic challenge. If there is significant left-to-right shunt, test occlusion of the duct with a balloon catheter, and if pulmonary arterial pressure drops, PDA closure can be considered after careful consideration at a specialized center (68). If Eisenmenger physiology is present, PDA closure is contraindicated.

The indication for catheter interventional closure of a left-to-right defect must be made in a specialized center in ACHD. If the indication is incorrect, shunt closure can worsen symptoms and prognosis.

For patients with severe PAH and vascular disease, the interventional creation of an ASD may be (69) or that of a shunt from the pulmonary artery to the descending aorta

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Table 1 Current recommendations for the treatment of ASD and VSD to reduce left-to-right shunting according to 2022 ESC/ERS guidelines (9)

Class I recommendation
❖ ASD closure is recommended in patients with evidence of right ventricular volume overload due to significant left-to-right shunting and PVR <3 WU and no evidence of left heart disease
◆ If left heart disease is suspected, balloon test occlusion of the defect with measurement of LV filling pressures is recommended and the benefit of shunt reduction by ASD closure (total or with fenestration) must be carefully weight against the risk LV filling pressure increase
❖ VSD closure is recommended in patients with evidence of LV volume overload due to significant left-to-right shunting and PVR <3 WU
Class IIa recommendation
❖ ASD closure should be considered in patients with significant left-to-right shunting (Qp/Qs >1.5) and PVR between 3 and 5 WU
❖ VSD closure should be considered for patients with significant left-to-right shunting (Qp/Qs >1.5) and PVR between 3 and 5 WU
Class IIb recommendation
❖ Fenestrated ASD closure may be considered in patients with PVR ≥5 WU in patients with significant left-to-right shunting (Qp/Qs >1.5) should PVR fall below 5 WU on targeted PAH treatment
❖ VSD closure may be considered in experienced centres for patients with VSD and significant left-to-right shunting (Qp/Qs >1.5) with PVR ≥5 WU
Class III recommendation
❖ VSD and ASD closure is contraindicated in patients with Eisenmenger physiology (right-to-left shunting across the defect leading to cyanosis at rest or during exercise)
❖ VSD and ASD closure is contraindicated in patients with PVR ≥5 WU and no significant left-to-right shunting

ASD, atrial septal defect; VSD, ventricular septal defect; ESC, European Society of Cardiology; ERS, European Respiratory Society; PVR, pulmonary vascular resistance; WU, Wood units; LV, left ventricular; Qp/Qs, pulmonary to systemic blood flow.

("reversed Potts shunts") may be considered to improve systemic CO and, correspondingly, systemic oxygen delivery and to make it more independent of pulmonary blood flow (70,71). These procedures are risky and reserved for specialized centers.

Recommendations for PAH in congenital left heart disease (group 2) in ACHD

Acquired left heart disease is the most common cause of PH (72).

Postcapillary PH may underlie any pathology leading to an increase in pulmonary venous and/or left atrial pressure (subsystemic obstruction, systolic/diastolic dysfunction).

Special risk at:

- ❖ Patients with transposition of the great arteries after atrial switch;
- ❖ Borderline small left-sided cardiac structures and restrictive ventricular physiology (Shone complex/ borderline hypoplastic left heart) (73).

Even if isolated postcapillary PH exists initially, a combined pre- and postcapillary problem often develops during the course, with increasing burden on the subpulmonary ventricle (73).

In PH group 2, it is imperative to focus on treatment of the underlying pathology associated with CHD by drug, interventional, or surgical interventions.

Routine use of targeted PAH medication does not seem justified even in CHD with isolated postcapillary PH. Combined P(A)H is challenging to treat because both components of P(A)H must be considered. If precapillary PAH exists in addition to the postcapillary component after optimization of hemodynamics and adequate heart failure therapy, specific PAH medication can be considered under close monitoring at specialized ACHD centers, although this can potentially worsen the clinical situation (74). In fact, initiating PAH medication in the presence of high pulmonary wedge pressure (indicating a postcapillary component) should be avoided as it may lead to pulmonary congestion (75).

Recommendations for PAH in univentricular heart

In univentricular hearts, the Fontan circulation is the

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surgically created state of palliative circulatory separation with only one functional subaortic ventricle. In patients with Fontan physiology, determination of mean pulmonary artery pressure (mPAP), mean pulmonary capillary wedge pressure (mPCWP), and pulmonary vascular resistance index (PVRI) are critical for assessing hemodynamics and differentiating causes in Fontan failure. Recently, it has also been shown with invasive stress testing that mPAP and mPCWP increase excessively and often meet the new criteria for postcapillary stress-PH, especially with increasing age (76).

Whether treatment with pulmonary vasodilators (PDE5is, ERA) is useful for patients who exceed the thresholds for pulmonary vascular disease remains unproven. Smaller studies of improvement of systolic dysfunction with ACE inhibitors have not been successful in Fontan patients, although in everyday life many patients are probatorily adjusted to these drugs. Studies on the improvement of myocardial diastolic dysfunction with spironolactone or SGLT2 inhibitors are not yet available.

As a "last resort", interventional fenestration of the Fontan circuit is also possible.

Interventional therapy for ACHD

A Potts shunt (a surgically or interventional placed connection between the left pulmonary artery and the descending aorta) or BAS has been described as helpful, particularly in children with severe PAH, for decompressing the pulmonary circulation and increasing systemic CO. In ACHD, there is virtually no experience with this procedure.

The performance of pulmonary artery denervation (PADN) has been described as a newer therapeutic approach. Although potentially promising, PADN should be considered experimental, especially in ACHD.

Intensive care measures in ACHD

The principles of intensive therapy in PAH were first included in the ESC/ERS guidelines in 2015 and revised in 2022. Prognosis and general principles of therapy of patients with late corrected CHD or IPAH are comparable. In patients with ES, numerous special features have to be considered.

Due to the high mortality of this patient group, treatment of concomitant diseases should also take place in specialized centers if possible.

Monitor right ventricular function by monitoring pressure and saturation centrally venous, echocardiography, NT-proBNP, troponin and lactate, right heart catheterization if necessary.

Therapy of anemia, arrhythmias, infections. Management of fluid balance (diuretics) while avoiding systemic hypotension and maintaining mean systemic blood pressure above 60 mmHg, using inotropics and vasopressors if necessary. Avoid intubation and invasive ventilation if possible.

Individualize specific PAH medication regimen, including intravenous/subcutaneous prostacyclin analogues as appropriate.

Interventional procedures only in specialized centers with appropriate experience, where mechanical circulatory support (veno-arterial ECMO, ECLS) is also possible as a bridge to transplantation or recovery. Depending on the possibilities and experience of the center and the patient's situation, individual decisions are made. Any escalation of therapy must be carefully weighed in the context of the overall prognosis (multimorbidity). Long-term management by right ventricular assist device (RVAD) [analogous to LV assist device (LVAD) for the left heart] has not yet been established in terminal right ventricular failure. Recently, however, there have been reports about using percutaneous devices (Protek Duo) long-term in PH patients with right heart failure as a bridge to transplant (77).

Connection to a qualified ACHD center

Patients with PAH require highly specialized and comprehensive diagnostic, therapeutic, and adjunctive management. Specialized centers of expertise can deliver optimal outcomes in terms of patient satisfaction, complication rates, hospital length of stay, and resource utilization.

In Germany, quality guidelines have existed since 2004, according to which specialized centers for the care and treatment of ACHD were created and physicians were specially trained and certified. With the 2018 model advanced training regulations, this additional training was structured and legalized, and PAH in ACHD is an integral part of it. Currently, there are more than 300 such specialists and 34 specialized institutions in Germany, including 21 supraregional ACHD centers, five ACHD focus hospitals, and eight ACHD focus practices. Analogous to ESC guidelines, supraregional ACHD centers are multidisciplinary with cardiologists, pediatric cardiologists, ACHD cardiac surgeons, pulmonologists, radiologists,

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and other specialties, as well as specialized nurses and psychosocial staff. They are committed to clinical research, participation in quality assurance, registries and trials, and education and training. To date, no minimum numbers have been established, but already national ACHD centers exceed the numbers suggested in the ESC guidelines (more than 200 patients per year screened for PH, more than 50 ACHD patients with PAH followed up and followed up on an ongoing basis).

Because of the close link between pediatric heart centers and ACHD centers, children and adolescents with CHDs and PAH also benefit from this system (diagnosis, risk adjustment, and therapy less evidence-based than in adults, extrapolation from their treatment algorithms, smooth transition possible, avoidance of gaps in care).

Conclusions

Knowledge gaps and future prospects

Studies on the therapy of PAH in patients with CHD (PAH-CHD) are limited. Since relevant prospective therapy studies usually include only a few patients with simple shunt lesion after defect closure and complex CHD patients are hardly included, it remains unclear who benefits from targeted PAH therapy. Prospective randomized trials are needed in this disease group.

For the future, the guidelines recommend using new signaling pathways to modulate PVR or PADN and investigating them in larger prospective randomized trials.

Because there is a close relationship between right heart, pulmonary vascular bed, and left heart in PAH-CHD, effects of reverse LV remodeling by modern heart failure therapy [angiotensin receptor-neprilysin inhibitor (ARNI), SGLT2 inhibitors] should also be clarified. The effects of PDE5is in patients with heart failure with preserved ejection fraction (HFpEF) and combined post- and precapillary PH (CpcPH) mentioned in the guidelines need to be awaited.

Clarification is also needed regarding whether examinations of pulmonary pressure and resistance during exercise (stress echocardiography, belated right heart catheterization) in PAH-CHD provide early evidence of pulmonary vascular disease and imply early therapy.

Analysis of ventricular function requires multimodality imaging in appropriate centers, especially in patients with complex cardiac anatomy.

For appropriate risk stratification of patients with PAH-CHD, more complex stratification models that also take into account CHD severity, subpulmonary (and systemic) ventricular function, and comorbidities should be tested in sufficiently large cohorts (78).

For patients with advanced disease, the option of mechanical circulatory support and heart and/or LTx must be explored at highly specialized, centers.

Finally, specialized care for ACHD with and without PAH by specialists in practices and clinics must be further expanded in cooperation with patient associations and brought to the attention of those affected (78,79).

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