Pulmonary hypertension in adults with congenital heart disease and Eisenmenger syndrome: current advanced management strategies

Michele D'Alto,[1] Gerhard-Paul Diller[2]

[1]Department of Cardiology, Second University of Naples, Monaldi Hospital, Naples, Italy
[2]Department of Cardiology and Angiology, Adult Congenital and Valvular Heart Disease Centre, University of Münster, Muenster, Germany

Correspondence to
Dr Michele D'Alto, Via T. di Camaino, 6, Naples 80128, Italy; mic.dalto@tin.it

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ABSTRACT

The presence of pulmonary arterial hypertension (PAH) increases morbidity and reduces survival in patients with congenital heart disease (CHD). PAH-CHD is a heterogeneous condition, depending on the type of the underlying defect and previous repair strategies. There is growing evidence of the benefits of PAH-specific therapy in the PAH-CHD population, but despite recent advances mortality rates remain relatively high. In the last years, an increasing focus has been placed on patients with PAH-CHD and net left-to-right shunt. Currently, there are limited data to guide the management of these patients and uncertainty on the cut-off values for eventual defect closure. Pregnancy conveys significant risks in PAH-CHD patients: appropriate counselling and care, including psychological support and a multidisciplinary team, should be part of the routine management of women with PAH-CHD of reproductive age. Some subgroups, such as patients with Down's syndrome, Fontan circulation and 'segmental' pulmonary hypertension, present particular challenges in terms of management and therapy. The current review focuses on contemporary treatment strategies in PAH-CHD patients with particular emphasis on challenging patient groups and conditions.

INTRODUCTION

Patients with congenital heart disease (CHD) increasingly reach adult age.[1] Despite earlier interventional or operative therapy, a considerable number of CHD patients still develop pulmonary arterial hypertension (PAH).[2] This is associated with increased morbidity and mortality. Depending on the type of the underlying defect and previous repair strategies, patients can present with heterogeneous anatomy and pathophysiology.[3] These differences are not purely academic but impact on treatment strategies. The current review focuses on contemporary treatment strategies in PAH-CHD patients with particular emphasis on challenging patient groups and conditions. Details on definition, epidemiology and pathophysiology of PAH-CHD have been previously published[4] and are not discussed here. Similarly, the classification of the condition is only reviewed as required for therapeutic decisions.

The extreme end of the spectrum of PAH in the setting of CHD is Eisenmenger syndrome.[4] This is characterised by pulmonary arterial pressure (PAP) elevated to (near-)systemic levels with shunt reversal, cyanosis and multiorgan involvement. On the other end of the spectrum are patients with PAH who have only small, insignificant shunt lesions unlikely to cause PAH in isolation (ie, PAH with coincidental cardiac defects), or patients with PAH who had undergone surgical or interventional closure of cardiac defects. These patients resemble those with idiopathic PAH (IPAH) and—by and large—benefit from similar treatment strategies. Currently, the most challenging group is, however, represented by patients with PAH, patent shunt lesions and predominantly systemic-to-pulmonary shunt flow at rest and during exercise. In this setting, the role of shunt closure and that of targeted PAH-specific therapies has not been fully established. While not falling within the current definition of PAH, several patients with CHD develop pulmonary vascular disease and may occasionally benefit from targeted PAH-specific therapies. These include patients after Fontan palliation or with complex CHD and segmental pulmonary hypertension. Owing to the challenging management of these patients (high mortality and morbidity) and the emerging role of targeted PAH therapies in this setting, these two groups are also discussed in this review.

CURRENT THERAPIES

Supportive therapy

General measures and supportive therapies recommended for PAH-CHD patients include regular assessment by trained and experienced PAH-CHD physicians, avoidance of pregnancy and adequate contraceptive measures, endocarditis prophylaxis, regular immunisation against influenza and pneumococcal infections as well as diagnosis and treatment of iron deficiency (especially in cyanotic patients).[3 5] Patients with PAH-CHD also benefit from symptomatic treatment with diuretics if signs or symptoms of heart failure occur. In addition, even supraventricular arrhythmias may be poorly tolerated in this setting and should be addressed proactively. Patients should avoid strenuous exercise, especially sports with high static demands.[3 6] However, regular physical activity within symptom limits is recommended and there are emerging data on potential beneficial effects of supervised exercise training and rehabilitation.[7] Patients with other coexisting indications such as atrial fibrillation and intrapulmonary thrombi in the absence of haemoptysis should be anticoagulated. However, a recent study found no conclusive evidence of a beneficial effect in terms of outcome in patients with PAH of non-IPAH aetiology.[8] Anticoagulation may also decrease iron reserves, thus affecting outcome in Eisenmenger patients.[9] Therefore, anticoagulation cannot be routinely recommended and should be

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reserved to selected PAH-CHD patients. Similarly, nocturnal oxygen therapy has been explored in Eisenmenger patients and was found to have no significant effect on haematology, exercise capacity or quality of life variables.[10] As a consequence, it is not routinely recommended in this setting.[11]

Specific medical therapy

Unlike in IPAH, the role of acute vasoreactivity testing and subsequent therapy with calcium channel blockers has not been established in PAH-CHD patients. The mainstay of therapy is, therefore, targeted PAH therapies. These currently include three groups of substances: (1) endothelin receptor antagonists (ERAs), (2) phosphodiesterase type 5 inhibitors (PDE-5i) and (3) prostanoids. While other substances (such as soluble guanylate cyclase stimulators and tyrosine kinase inhibitors) are currently undergoing clinical investigation, their role in PAH-CHD has not been established.

A pathologically elevated PAP—in isolation—does not necessarily imply the presence of pulmonary vascular disease in CHD patients. Rather, this finding could be due to elevated left atrial pressures (left-sided diastolic dysfunction and valvular heart disease are not uncommon in CHD patients) or could merely reflect high pulmonary blood flow in the presence of significant left-to-right shunt (postcapillary pulmonary hypertension). Therefore, in this setting pulmonary vascular resistance (PVR) and transpulmonary gradient must be calculated before initiating targeting PAH therapies.

Therapeutic algorithms depend on the underlying form of PAH-CHD (table 1).

Patients with postoperative PAH or with only small coincidental cardiac defects are pathophysiologically very similar to patients with IPAH. Therefore, these patients should be treated according to current PAH guidelines. Figure 1 illustrates a possible treatment algorithm depending on the clinical severity of the condition.

To guide therapy, adequate treatment goals need to be established a priori. These could relate to invasive haemodynamic parameters, such as cardiac output or right atrial pressure, functional parameters, mainly 6-min walk distance, or right ventricular function based on cardiac imaging or neurohormonal peptide levels.[3] Unfortunately, appropriate treatment goals have not been established yet for this cohort, which differs significantly from iPAH and other types of PAH. This is especially true for patients with Down's syndrome. If an adequate response cannot be achieved with monotherapy, escalation of therapy should be considered.

Patients with Eisenmenger physiology present with a multisystem disorder affecting different organ systems and leading to a multitude of complications. The main aim of medical therapy has traditionally been focused on symptom improvement. A multicentre, double-blind, randomised, placebo-controlled study has shown that treatment with the ERA bosentan over 16 weeks leads to significant improvement in 6-min walk distance and haemodynamics.[12] Subsequently, a considerable number of observational studies have corroborated these findings, showing improvements in functional capacity as well as oxygen saturation over the mid- to long-term. Therefore, to date, the most robust evidence for using targeted PAH therapies in Eisenmenger patients exists for bosentan. In addition, two recent studies have addressed the long-term impact of targeted PAH therapies in Eisenmenger patients.[13 14] These studies have confirmed a sustained improvement in functional class and 6-min walk distance in the long term. As a consequence, current guidelines support the use of bosentan in Eisenmenger patients in New York Heart Association (NYHA) class 3 (Class IB recommendation).[11] While less robust compared with bosentan (guideline recommendation IIaC), increasing evidence is emerging on the beneficial effects of PDE-5i in Eisenmenger syndrome patients. This includes an observational study by Zhang *et al* including 168 Eisenmenger patients treated with open-label sildenafil for 1 year. The study showed significant improvements in pulmonary haemodynamics (including PVR and mean PAP) as well as in symptoms, peripheral oxygen saturation and 6-min walk distance.[15] In addition, Mukhopadhyay *et al*[16] reported data from 16 Eisenmenger patients showing that the PDE-5i tadalafil reduces PVR, mean PAP and increased peripheral oxygen saturation after 12 weeks of therapy.

There is comparably limited information on the effect of combination therapy in Eisenmenger patients. While a methodologically robust prospective, randomised double-blind crossover study in 21 Eisenmenger patients showed no significant improvement in exercise capacity in stable Eisenmenger syndrome patients started on sildenafil in addition to bosentan,[17] two more recent observational studies in patients deteriorating on targeted PAH monotherapy were able to demonstrate significant improvements in exercise capacity and haemodynamics.[14 18] Furthermore,

Table 1 Clinical classification of PAH in CHD and treatment principles

Clinical classification of PAH in CHDs	Treatment strategy
PAH with clinically not relevant L-R shunt: L-R shunt through small defects (usually VSD <1 cm or ASD <2 cm) with a clinical picture very similar to IPAH	Pathophysiologically similar to IPAH Patients frequently included in landmark IPAH trials
PAH after corrective cardiac surgery: Corrected (closed) shunt, but PAH still present immediately after surgery or recurred months or years after surgery, in the absence of significant postoperative residual shunt	Treatment principles similar to IPAH with the exception of use of calcium channel blockers and anticoagulation. For both strategies, conclusive data in the setting of PAH-CHD are lacking
PAH associated with relevant L-R shunt (systemic-to-pulmonary): L-R shunt through moderate to large defects, with mild to moderate increase in PVR, with no cyanosis	Heterogeneous group of patients. Limited data/uncertainty on the cut-off values for defect closure. No data on the long-term effects of targeted PAH therapies in the setting of large defects with relevant systemic-to-pulmonary shunts
Eisenmenger syndrome, shunt reversal (pulmonary-to-systemic): L-R shunts due to large defects leading to a severe increase in PVR and resulting in a reversed R-L or bidirectional shunt with cyanosis, high haemoglobin and multiple organ involvement	Extreme end of the spectrum of PAH in the setting of CHD. Multiorgan disease. Symptomatic benefit of targeted PAH therapies over short- to mid-term well established (at least in NYHA class ≥3). Potential survival benefit from targeted PAH therapies (but only limited data at present)

ASD, atrial septal defect; CHD, congenital heart disease; IPAH, idiopathic pulmonary arterial hypertension; L-R, left-to-right; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; R-L, right-to-left; VSD, ventricular septal defect.

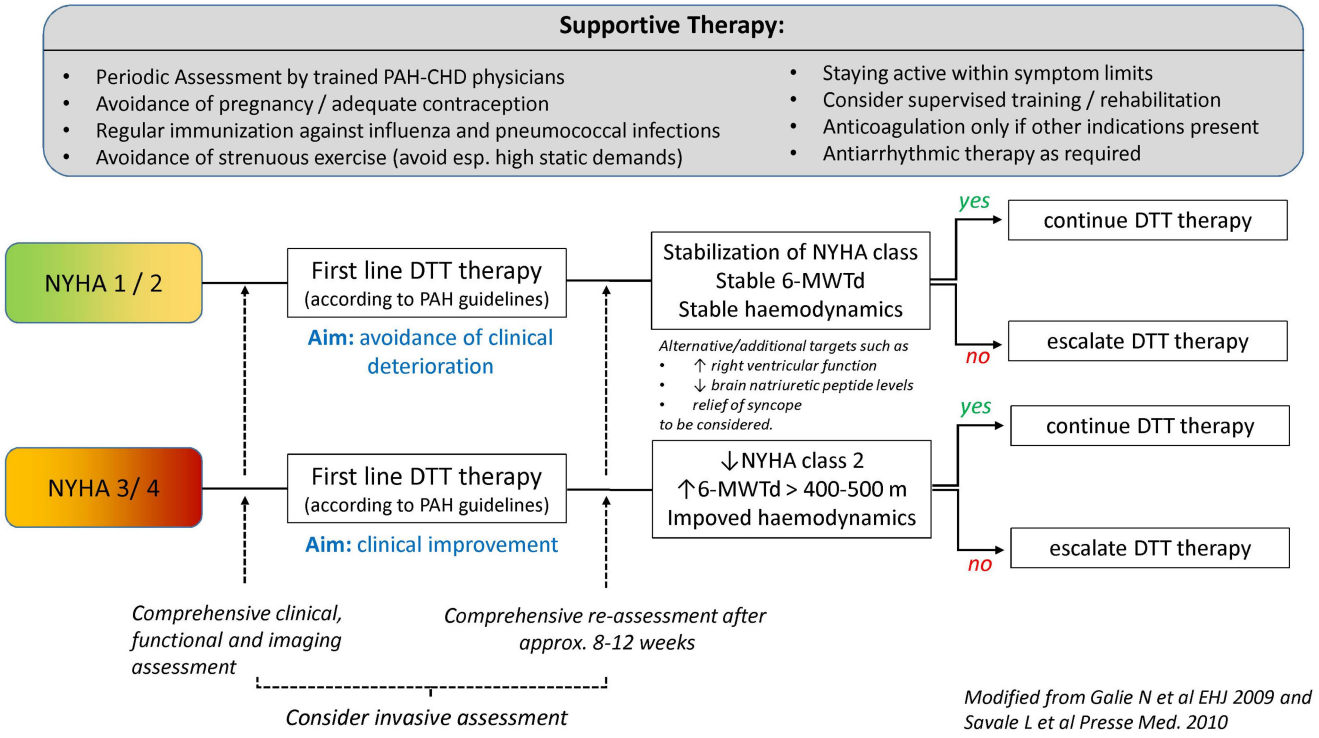

Figure 1 Suggested treatment algorithm for patients with PAH-CHD with closed or coincident (small) shunt lesions. Several recommendations for supportive therapy are mainly based on expert opinion and expand those provided by current guidelines on the management of pulmonary hypertension. 6MWTd, 6-min walk test distance; CHD, congenital heart disease; DTT, PAH-specific disease targeting therapies; PAH, pulmonary arterial hypertension.

earlier initiation of targeted therapies (eg, in NYHA class 2) may be beneficial in patients with Eisenmenger syndrome as it is in those with IPAH.[19] The ongoing trial of the new ERA macitentan in patients with Eisenmenger syndrome, also including NYHA class 2 patients, may provide further information on the utility of medical therapy in this setting.[20]

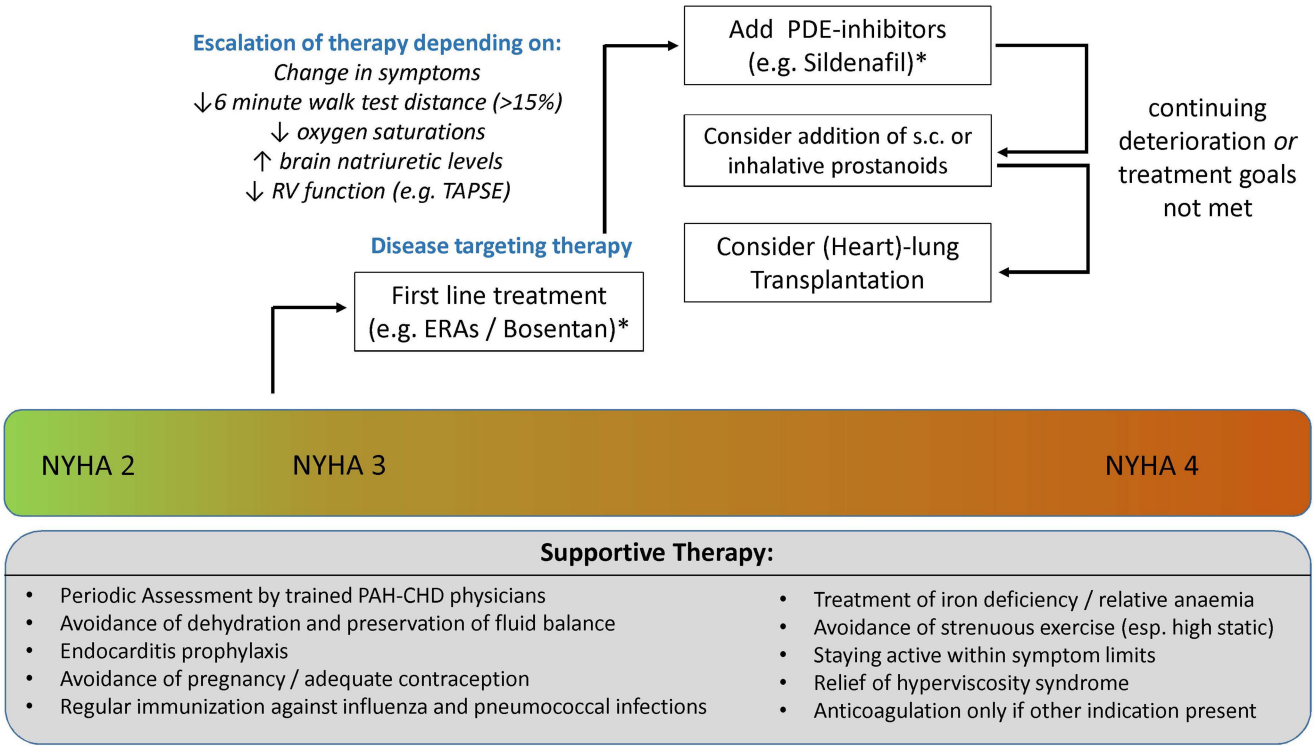

Figure 2 Suggested treatment algorithm for patients with Eisenmenger syndrome. CHD, congenital heart disease; ERAs, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; TAPSE, tricuspid annular plane systolic excursion. *Depending on preference and country-specific licensing situation, phosphodiesterase (PDE) inhibitors may also be considered as first line medication.

Emerging evidence suggests that targeted PAH therapies may also have a beneficial effect on survival in Eisenmenger patients. Dimopoulos *et al*[21] have assessed survival prospects of Eisenmenger patients with and without targeted therapies retrospectively. In a cohort of 229 patients they found that even after adjustment for baseline characteristics, treated patients had better survival prospects compared with those not on targeted therapies. These findings await further confirmation but have recently been supported by a smaller study investigating the impact of sildenafil therapy in patients with Eisenmenger syndrome.[22]

Figure 2 illustrates a possible treatment algorithm for Eisenmenger patients. It shows that depending on treatment response (especially further deterioration despite monotherapy), the addition of a second drug should be considered.

PAH ASSOCIATED WITH LEFT-TO-RIGHT SHUNT

Repair of cardiac defects in the presence of overt pulmonary vascular disease is contraindicated. In fact, patients who develop PAH after shunt closure have a worse prognosis than patients with uncorrected PAH-CHD.[23 24] This has raised appropriate concerns regarding correction of congenital heart defects in patients with overt PAH. However, patients with 'borderline' haemodynamics and mild-to-moderate degrees of pulmonary vascular disease remain a particularly challenging subgroup, as strict criteria for determining operability cannot established. The current European grown-up CHD guidelines[11] suggest a Qp/Qs >1.5 and a PVR <5 Wood units as the haemodynamic upper limits for operability in patients with atrial or ventricular septal defects, thus discouraging shunt closure in the presence of severe PAH or Eisenmenger syndrome. The guidelines,[11] however, also define a 'grey zone' where PAP or PVR is high but <2/3 of systemic values (baseline, with acute vasodilator testing, or after targeted PAH therapy). There are arguments in favour and against repair of congenital heart defects in patients with preserved net left-to-right shunt in this haemodynamic 'grey zone'.[25] It is worth noting, however, that the recent recommendations from the 5th World Symposium on Pulmonary Hypertension suggest a more cautious approach, not advocating defect closure in patients with PVR >4.6 Wood units.[26] A recent retrospective study assessed haemodynamics in a consecutive cohort of patients with persistent PAH after shunt closure. All patients had mean PAP ≥25 mm Hg and 21/22 (95%) PVR index ≥6 Wood units*m^2 at baseline evaluation. In this series, baseline PVR ≥5 Wood units, PVR index ≥6 Wood units*m^2 and pulmonary to systemic vascular resistance ratio ≥0.33 were common findings in patients who developed PAH late after shunt closure.[27]

In the last years, there has been increasing interest in the potential for use of PAH-specific therapies, the so-called 'treat-and-repair' strategy, aimed at reducing PVR, thus improving operability of patients with PAH-CHD. However, available data on closure of intracardiac or extracardiac shunts in the presence of severe PAH are scarce and still limited to case reports or case series (mostly from patients with pretricuspid defects and borderline haemodynamics). Initial results appear promising, but in most cases follow-up was short, and the long-term adaptation of the RV and the pulmonary circulation after correction of the congenital heart defect remain unknown.

Currently, there are no established markers of reversibility in this therapeutic 'grey zone', nor evidence-based algorithms to guide assessment for operability in these patients, and decisions should be based on careful clinical and haemodynamic evaluation of the individual patient. Assessment of such patients should be performed in tertiary centres with expertise in CHD and PAH.

PARTICULAR CONDITIONS

The following paragraphs discuss some selected clinically challenging scenarios in the setting of PAH-CHD.

Pregnancy and contraception

Pregnancy conveys significant risks both for the mother and child in PAH-CHD patients and is contraindicated.[28] A systematic review of pregnancies in patients with different forms of pulmonary hypertension showed that maternal mortality occurs in 17% of IPAH and in 28% of PAH-CHD patients.[29] In particular, the use of general anaesthesia was associated with a four-fold higher risk of death (OR 4.37, p=0.02).

Patients should be advised against pregnancy and reminded that even termination of pregnancy carries significant risks. Women with PAH-CHD who become pregnant require treatment by a multidisciplinary team. The crucial issue is risk assessment and decision with the patient on whether to continue or terminate the pregnancy. In general, the risk of complications is correlated with disease complexity. Nevertheless, if the patient decides to continue the pregnancy, careful follow-up should be conducted in centres with appropriate expertise in pulmonary hypertension, CHD, anaesthesia and intensive care, so as to minimise complications. ERAs and warfarin must be discontinued for their potential foetal toxicity and PDE-5i, prostanoids and low-molecular-weight heparin (if anticoagulation is required) should be considered. Inhaled nitric oxide may be used in the intensive care unit if a pulmonary hypertensive crisis occurs, in particular in the peri-delivery period.

Dual contraception must be advised for patients on treatment with ERAs, especially bosentan, in view of the interaction with progesterone-based compounds. Oestrogen-containing compounds should be avoided due to the increased risk of thrombosis. Intrauterine devices are effective, but convey a certain risk of infection and endocarditis. Appropriate counselling and care, including psychological support, should be part of the routine management of all women with PAH-CHD of reproductive age.

Pulmonary hypertension in patients with Down's syndrome

The prevalence of CHD in the Down's population is 40%–60%, and atrioventricular septal defect is the most commonly occurring CHD (~30%–50%).[30] Children with Down's syndrome may develop progressive pulmonary changes earlier than non-Down's individuals with similar congenital heart defects, probably due to intrinsic endothelial dysfunction of the pulmonary vascular tree,[31] but may also show recurrent pulmonary infection, decreased alveolar density or macroglossia causing chronic upper airway obstruction.

Few data and no randomised clinical trials are available at present on the efficacy of PAH-specific therapy in patients with PAH-CHD and Down's syndrome. Two recent papers from the same group[32 33] suggested that oral bosentan therapy is safe and well tolerated in adult patients with CHD-related PAH and Down's syndrome, with no change in quality of life during treatment. Nevertheless, the results of the 6-min walk test (6MWT) were conflicting. Also the validity of 6MWT in patients with Down's syndrome is arguable (poor compliance in many patients) and 6-min walk distance relates more to intellectual disability than cardiorespiratory fitness.[34]

More recently, D'Alto *et al*[35] assessed the safety and long-term effects of oral bosentan in adult patients with PAH-CHD

with and without Down's syndrome. The authors observed that bosentan was safe and clinical status, exercise tolerance and pulmonary haemodynamics improved, regardless of the presence of Down's syndrome during 12 months of treatment.

Box 1 Key issues in PAH-CHD particular conditions

Borderline haemodynamics
- Safety limits for shunt closure: Qp/Qs >1.5 and PVR ≤5 Wood units (or PVR index ≤6 Wood units*m^2)
- Arguments in favour and against repair of CHD in patients with still net left-to-right shunt and 'borderline' haemodynamics
- Patients developing PAH after shunt closure have a poor prognosis
- Decisions on shunt closure must be based on careful clinical and haemodynamic evaluation of the individual patient (not on procedure feasibility)
- Efficacy of 'treat-and-repair' strategy is not well established

Segmental PAH
- Definition: complex CHD with hyperperfused areas (developing PAH)
- Difficult diagnosis requiring a high degree of suspicion and heart catheterisation performed in specialised CHD centres
- Efficacy of PAH-specific therapy is not established

Fontan patients
- The absence of an RV pumping into the pulmonary circulation requires very low pulmonary arterial pressure (PAP) and PVR
- Fontan patients usually do not fulfil standard criteria for PAH having often normal mean PAP (<25 mm Hg), low cardiac index and high PVR (>3 Wood units)
- PVR is the major determinant of circulatory output
- Drugs able to reduce PVR (ie, PAH-specific drugs) appear as an attractive option but their efficacy is not well established

Pregnancy
- Consider pregnancy as a high risk condition (PAH-CHD maternal mortality 25%–30%)
- Discouraging pregnancy and advising for contraception are important features of PAH-CHD management
- High risk for general anaesthesia
- Need for multidisciplinary team for following pregnant PAH-CHD patients

Down's syndrome (DS)
- High prevalence of CHD (about 50%)
- Pulmonary vascular disease development earlier than non-DS patients
- Multiple mechanisms contributing to the development of PH/PAH (endothelial dysfunction, recurrent pulmonary infection, decreased alveolar density, macroglossia causing chronic upper airway obstruction)
- Surgical and medical undertreatment of DS patients
- Few data on the efficacy and safety of PAH-specific therapy
- Difficult evaluation at follow-up (ie, risks related to general anaesthesia for right heart catheterisation; reliability of 6MWT and quality of life questionnaires)

6MWT, 6-min walk test; CHD, congenital heart disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

Many unsolved concerns, however, such as ethical issues, the validity of 6MWT, the reliability of quality of life questionnaires and the risks related to invasive assessment (frequent need for general anaesthesia, difficulties with intubation) remain and make the evaluation of Down's syndrome patients very complex.

Segmental PAH

In some patients with complex CHD, such those with truncus arteriosus with stenosis of the left or right pulmonary artery, it may possible to have hyperperfused areas while other lung areas are normally or hypoperfused. In these cases, pulmonary vascular disease may involve only part rather than the entire lung vasculature, resulting in 'segmental PAH' (ie, pulmonary vascular disease involving a single lung or single areas). Also segmental pulmonary artery stenoses and multiple major aortopulmonary collateral arteries (MAPCAs), commonly observed in complex pulmonary atresia, often result in segmental PAH.[36] This condition may affect large areas of the lungs (ie, the MAPCAs' supplied pulmonary areas) contributing to cyanosis and exercise intolerance.

The diagnosis of PAH in this setting requires a high degree of suspicion and great expertise to understand whether low oxygen saturations in patients with MAPCAs are attributable to segmental PAH or inadequate lung perfusion as a result of inadequate pulmonary blood flow from MAPCAs, MAPCA stenosis or thrombosis, shunt patency, and so on. The presence of severe cyanosis, shortness of breath and the echocardiographic evidence of low velocity shunting through the MAPCAs increases the suspicion of segmental PAH.[36] The diagnosis of segmental PAH can only be confirmed on cardiac catheterisation, best performed in specialised CHD centres.

Nowadays, there are few preliminary, but emerging data supporting the use of specific therapy for PAH in this setting. Recently, a small retrospective case series of seven patients with complex pulmonary atresia treated with oral bosentan has reported a significant improvement of functional class and exercise capacity in these patients having segmental PAH.[37] Further larger and prospective studies are needed for confirming the efficacy and safety of PAH-specific therapy in this setting.

Fontan patients

A Fontan circuit (atrio- or cavopulmonary connections), used to palliate 'single ventricular' heart defect, involves the creation of a right-sided circulation without the interposition of a ventricle. The presence of low PAP and PVR allowing passive flow of blood through the lungs without an excessive rise in central venous pressures are essential for this circulation. Even small rises in PAP, PVR or left atrial pressure can cause failure of the 'Fontan' circulation with devastating effects (congestive heart failure, ascites, protein losing enteropathy, low cardiac output, arrhythmias and eventually death). Unfortunately, PVR may often be high in adult Fontan patients, despite a low PAP and low trans-pulmonary gradient, because of very low pulmonary blood flow.[36] Because PVR is the major determinant of circulatory output, good long-term outcome in Fontan patients requires a low PVR.

Despite the fact that Fontan patients do not usually fulfil standard criteria for PAH, specific PAH drugs aimed at reducing PVR appear as an attractive option. Even with some initial evidence of potential clinical response to PAH-specific therapies in Fontan patients using oral sildenafil,[38] two randomised trials have failed to demonstrate an increase in exercise capacity with PAH-specific therapy.[39 40] Therefore, nowadays, there is no

sufficient evidence suggesting that PAH therapies are beneficial in patients with a failing Fontan circulation due to raised PVR and further exploration is needed before sound therapeutic recommendations can been made.

CONCLUSIONS

Advances in the diagnosis of CHD and its surgical and medical management have significantly increased the number of patients surviving into adulthood. The best therapy for PAH-CHD remains prevention by timely repair of the defect. The development of PAH, and particularly Eisenmenger syndrome, in these patients is associated with increased morbidity and mortality. There is growing evidence of the benefits of PAH-specific therapy in PAH-CHD patients. Specific issues exist with regard to the management of certain patient subgroups or conditions (box 1).

Pregnancy carries significant risks in PAH-CHD patients. Important aspects of PAH-CHD management are early advice on potential risks related to pregnancy and patient education regarding contraception. Patients with Down's syndrome represent a significant proportion of the PAH-CHD population, but historically they have been managed suboptimally. Although new and encouraging data are emerging, there remains a need for further investigations. Regarding patients with intracardiac or extracardiac shunt and 'borderline' haemodynamics, there is still no conclusive evidence-based algorithm to guide assessment for operability, and decisions should be based on careful clinical and haemodynamic evaluation of the individual patient with a high degree of caution before closing the defect. The efficacy of PAH-specific therapy in patients with segmental PAH and in patients with Fontan correction, despite the promising initial reports, is not well established yet and warrants further investigation.

Overall, the field of PAH-CHD has seen dramatic progress over the last two decades with improved survival and quality of life for patients. However, this remains a deadly and debilitating disease that requires further research and a close collaboration between tertiary specialist centres and local non-specialist services to enable this young group of patients to fulfil their full life potential.

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Michele D'Alto and Gerhard-Paul Diller

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