Pulmonary arterial hypertension associated with congenital heart disease: classification and pathophysiology

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Abstract

While the development of pulmonary arterial hypertension is not uncommon in adult congenital heart disease patients, other forms of pulmonary hypertension (PH) may also be present. A good understanding of PH classification is therefore vital for clinicians managing adult patients with congenital heart disease. This paper reviews both the general classification of PH and more detailed approaches to classifying pulmonary arterial hypertension in association with congenital heart disease.

Keywords: Pulmonary hypertension, Pulmonary arterial hypertension, Congenital heart disease, Classification, Eisenmenger syndrome

Background

Pulmonary arterial hypertension (PAH) is not uncommon within the adult congenital heart disease (CHD) population, with estimates of prevalence ranging between 4.2–28% [1, 2]. Furthermore, other forms of Pulmonary Hypertension (PH) may also develop in CHD patients. Health care professionals who manage adult CHD patients, therefore, require in-depth understanding of the classification of PH in general and of the more detailed classification of PAH associated with CHD.

Pulmonary hypertension classification

Pulmonary hypertension has, until recently, been defined as the presence of a resting mean pulmonary arterial pressure (mPAP) of ≥25 mmHg at right heart catheterisation [3, 4]. More recently, the 6th World Symposium of PH (WSPH) has proposed two classification groups using lower mPAP thresholds: pre-capillary PH, as defined by mPAP > 20 mmHg and pulmonary vascular resistance (PVR) ≥3 Woods Units and left atrial pressure ≤15 mmHg (measured by the pulmonary arterial wedge pressure, left ventricular end diastolic pressure or directly), and post-capillary PH, defined by mPAP > 20 mmHg and left atrial pressure > 15 mmHg [5]. Previous guidelines also defined PH by a mPAP > 30 mmHg on exercise [6]. Although an abnormal increase in mPAP on exercise can be defined as mPAP/cardiac output > 3, it is not possible to reliably differentiate between pulmonary vascular disease and elevated left atrial pressure as the cause for this "abnormal" increase in pressure on exercise [7]. PH on exercise is not, therefore, part of current diagnostic criteria [5].

In addition to a haemodynamic approach, patients with PH can also be classified using a clinical approach which describes five groups with shared clinical and pathophysiological features (Table 1) [3]:

Group 1 (PAH) is characterised by a proliferative vasculopathy of the small pulmonary arteries resulting in increased pulmonary vascular resistance (PVR). PAH may be idiopathic (IPAH), may develop in patients exposed to various drugs and toxins (including amphetamines, amphetamine-related appetite suppressants, ...
beta-interferon and some tyrosine kinase inhibitors) [8] or may be associated with other conditions, including CHD, connective tissue disease, portal hypertension and human immunodeficiency virus (HIV). Estimates of the prevalence of PAH within adult CHD patients range between 4.2–28% [1, 2]. Approximately 20% of patients with PAH have a mutation in bone morphogenetic protein receptor-2 (BMPR-2), while 70% of patients with a family history of PAH also have this mutation; those patients with a BMPR-2 mutation and/or clear family history of PAH are described as having heritable PAH [9].

Group 2 (PH due to left heart disease, PH-LHD) may develop as a result of left ventricular systolic or diastolic dysfunction or valvular disease. In PH-LHD, raised pulmonary arterial pressure may develop purely due to passive “back-pressure” from the left heart (isolated post-capillary PH) or a secondary pulmonary arterial vasculopathy may be present (combined pre and post-capillary PH, typified by elevated left atrial pressure but a high PVR and/or diastolic pulmonary pressure minus mean wedge pressure, the diastolic pressure gradient) [10].

Group 3 (PH due to lung disease, PH-Lung) may be present in association with airways disease (e.g. chronic obstructive disease including emphysema), parenchymal disease (e.g. pulmonary fibrosis) and hypoventilation (e.g. neuromuscular disease and obesity hypoventilation) [11, 12].

Group 4 disease (chronic thromboembolic PH, CTEPH) occurs when there is impaired fibrinolysis of thromboembolic disease resulting in stenoses within the pulmonary arterial lumen [13].

Group 5 comprises conditions with uncertain or multiple possible aetiologies for the development of PH (including sarcoidosis, haemolytic anaemias and Langerhans Cell Histiocytosis).

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**Table 1** Pulmonary hypertension classification [3]. Forms of pulmonary hypertension directly due to congenital cardiac and/or pulmonary arterial defects in bold

| 1. Pulmonary Arterial Hypertension |
|-----------------------------------|
| 1.1 Idiopathic                    |
| 1.2 Heritable                     |
| 1.2.1 BMPR2 mutation              |
| 1.2.2 Other mutations             |
| 1.3 Drugs and toxins induced      |
| 1.4 Associated with:              |
| 1.4.1 Connective tissue disease   |
| 1.4.3 Portal hypertension         |
| 1.4.4 Congenital heart disease    |
| 1.4.5 Schistosomiasis             |

| 1*. Pulmonary veno-occlusive disease/capillary haemangiomatosis |
| 1*.1 Idiopathic                                                 |
| 1*.2 Heritable                                                 |
| 1*.2.1 EF2AK4 mutation                                         |
| 1*.2.2 Other mutations                                         |
| 1*.3 Drugs, toxins and radiation induced                       |
| 1*.4 Associated with:                                          |
| 1*.4.1 Connective tissue disease                               |
| 1*.4.2 HIV infection                                           |

| 1*. Persistent pulmonary hypertension of the newborn           |

| 2. Pulmonary hypertension due to left heart disease            |
| 2.1 Left ventricular systolic dysfunction                      |
| 2.2 Left ventricular diastolic dysfunction                     |
| 2.3 Valvular disease                                           |

| 2*. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies |

| 2*.1 Left ventricular systolic dysfunction                      |
| 2*.2 Left ventricular diastolic dysfunction                     |
| 2*.3 Valvular disease                                           |

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| 3. Pulmonary hypertension due to lung disease and/or hypoxia   |
| 3.1 Chronic obstructive pulmonary disease                      |
| 3.2 Interstitial lung disease                                  |
| 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern |
| 3.4 Sleep-disordered breathing                                 |
| 3.5 Alveolar hypoventilation disorders                         |
| 3.6 Chronic exposure to high altitude                         |
| 3.7 Developmental lung diseases                                |

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| 3*.1 Chronic obstructive pulmonary disease                      |
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| 3*.3 Other pulmonary diseases with mixed restrictive and obstructive pattern |
| 3*.4 Sleep-disordered breathing                                 |
| 3*.5 Alveolar hypoventilation disorders                         |
| 3*.6 Chronic exposure to high altitude                         |
| 3*.7 Developmental lung diseases                                |

| 4. Chronic thromboembolic disease and other pulmonary arterial obstructions |
| 4.1 Chronic thromboembolic pulmonary hypertension                |
| 4.2 Other pulmonary artery obstructions:                         |
| 4.2.1 Angiosarcoma                                               |
| 4.2.2 Other intravascular tumours                                |
| 4.2.3 Arteritis                                                  |
| 4.2.4 Congenital pulmonary arterial stenoses                    |

| 4*. Chronic thromboembolic disease and other pulmonary arterial obstructions |
| 4*.1 Chronic thromboembolic pulmonary hypertension                |
| 4*.2 Other pulmonary artery obstructions:                         |
| 4*.2.1 Angiosarcoma                                               |
| 4*.2.2 Other intravascular tumours                                |
| 4*.2.3 Arteritis                                                  |

| 4*.1 Chronic thromboembolic disease and other pulmonary arterial obstructions |

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**Table 1** Pulmonary hypertension classification [3]. Forms of pulmonary hypertension directly due to congenital cardiac and/or pulmonary arterial defects in bold (Continued)

| 4.2.5 Parasites (hydatidosis)                                     |
| 5. Pulmonary hypertension with unclear and/or multifactorial mechanisms |
| 5.1 Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy |
| 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis neurofibromatosis |
| 5.3 Metabolic disorders: glycerol storage disease, Gaucher disease, thyroid disorders |
| 5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension |
The precise form of PH impacts significantly not only on the optimal treatment (which may include PAH-specific therapies, intervention for CTEPH in the form of pulmonary endarterectomy or balloon pulmonary angioplasty or optimisation of treatment of underlying cardiorespiratory disease), but also on prognosis (Fig. 1) [14].

Pulmonary arterial hypertension associated with congenital heart disease

Patients with PAH associated with CHD (PAH-CHD) may be further classified in 2 main ways:

Clinical classification

First, a clinical classification comprising 4 groups can be described (Table 2) [3]. This classification system provides a clinically useful method of grouping patients with similar therapies and outcomes:

| Group | Description |
|-------|-------------|
| A. Eisenmenger Syndrome | Large congenital systemic-to-pulmonary shunt leading to pulmonary vasculopathy, increased PVR and reversal of shunt. Cyanosis and erythrocytosis present. |
| B. PAH associated with a predominant systemic-to-pulmonary shunt | Moderate-large shunt with mild-moderately increased pulmonary vascular resistance. Patient is not cyanotic at rest. Defect may be correctable or non-correctable. |
| C. PAH associated with a small defect | Significantly elevated pulmonary vascular resistance in the presence of a small defect (ASD < 2 cm diameter, VSD < 1 cm diameter). Often behaves similarly to idiopathic pulmonary arterial hypertension. |
| D. PAH associated with a repaired defect | PAH persists after closure or develops/recurs following closure. |

![Fig. 1](https://doi.org/10.1183/09031936.00078411) Survival of patients with PH is significantly related to the form of PH [14]. Abbreviations: PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PH-LHD, pulmonary hypertension associated with left heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; PH-lung, pulmonary hypertension associated with lung disease; PAH-SSc, pulmonary arterial hypertension associated with systemic sclerosis. Reproduced with permission of © ERS 2019: European Respiratory Journal 39 (4) 945–955; DOI: https://doi.org/10.1183/09031936.00078411 Published 31 March 2012
a. Group A (Eisenmenger Syndrome [ES]) is characterised by increased flow and pressure due to a large unrepaired systemic-to-pulmonary shunt resulting in the development of a pulmonary vasculopathy. Heath and Edwards described six histological grades of pulmonary vascular disease in ES, with progressive changes within the intima and media leading to narrowing of the pulmonary arterial bed (Fig. 2) [16]. This process results in increased PVR and subsequent shunt reversal, leading to cyanosis and subsequent secondary erythrocytosis. Subsequent studies have identified the importance of inflammation in the development of this vasculopathy, together with abnormal levels of endothelin, nitric oxide and prostacyclin [17].

b. Group B includes patients with moderate-to-large left-to-right shunts and is characterised by mild-to-moderately increased PVR in the absence of cyanosis. These shunts may be amenable to closure depending on both the PVR and the nature of the shunt.

c. Group C disease is characterised by small defects (atrial septal defect [ASD] < 2 cm diameter or ventricular septal defect [VSD] < 1 cm diameter, so-called bystander lesions), which are felt unlikely to be responsible for the development of PAH. In the context of significant established PAH, the defect acts to reduce right ventricular afterload by acting as a "relief valve" and should not be closed.

d. Group D consists of patients with the development or recurrence of PAH following the repair of a defect.

**Anatomical-pathophysiological**

The second form of classification of PAH-CHD is the anatomical-pathophysiological system (Table 3) [18]. This system uses 5 criteria to describe a lesion: type, size, shunt direction, associated abnormalities and repair status.

The anatomical-pathophysiological system may be used to complement and further refine the clinical classification system. Although as a whole, group A (ES) is associated with superior outcomes when compared with group D [19], patients with different underlying defects and ES are likely to have different outcomes. For example, patients with post-tricuspid defects have superior survival from diagnosis when compared with those with pre-tricuspid defects (Fig. 3) [20]. This presumably reflects better adaptation of the right ventricle, which has been pressure-loaded from an early age, with a persistent foetal phenotype [21]. The appreciation of poorer survival in those with pre-tricuspid defects may, therefore, stimulate earlier and more aggressive PAH treatment. The reason why a minority of patients with a large unrepaired atrial septal defect with initial volume-loading of the right heart develop ES is unclear; some groups have proposed a "second-hit" hypothesis, whereby an underlying genetic abnormality predisposes to the development of PAH [22].
Other forms of PH in association with CHD

As well as PAH, other forms of PH may develop in association with CHD (Table 1):

**Group 2**
PH in association with increased left heart filling pressures may develop for a variety of reasons due to CHD, including congenital left heart valvular disease, congenital left ventricular outflow tract obstruction and congenital pulmonary vein stenosis. PH-LHD may also develop in patients with CHD due to comorbid acquired heart disease, including acquired valvular disease and systolic or diastolic dysfunction unrelated to the CHD.

**Group 3**
Restrictive or obstructive pulmonary function is not uncommon in patients with CHD [23, 24]. Patients with congenital abnormalities may also develop acquired respiratory disease, for example the incidence of obstructive sleep apnoea in patients with Down syndrome is estimated to be > 50% [25].

**Group 4**
In situ thrombus may develop in 21% of patients with ES [26]. Although it is often mural and non-obstructive, pulmonary arterial obstruction may occur, which can further contribute to increased pulmonary vascular resistance. Congenital (peripheral) pulmonary arterial stenoses may also result in a rise in pulmonary artery pressures and right ventricular overload.

**Group 5**
Segmental PH is included in group 5 PH and is characterised by abnormal cardiovascular anatomy resulting in distal pulmonary vascular disease differentially affecting pulmonary segments. A typical example is tetralogy of Fallot with pulmonary atresia and aorto-pulmonary collaterals which often results in pulmonary vascular disease in some, but not all, segments of the lung [27].

**Fontan circulation**
Fontan procedures performed in patients with univentricular physiology result in a single circulation in which the pulmonary and systemic circulations run in series [28]. The ventricle is therefore committed to the systemic circulation while caval return is redirected to the pulmonary arteries without the support of a subpulmonary ventricle. This system requires low PVR to maintain preload of the single ventricle and systemic venous hypertension to drive blood through the pulmonary circulation. Pulmonary vascular remodelling is known to occur in patients with a Fontan circulation [29, 30]. Therefore, although patients with a Fontan circulation cannot develop PH as conventionally defined (mPAP ≥ 25 mmHg), an increase in PVR may develop with adverse effects on functioning of the circulation [28]. Pulmonary vasodilator therapies may therefore sometimes be used even though definitive evidence regarding efficacy, timing and type of therapy to use in this cohort remains controversial [31–33].
**Conclusion**

A good understanding of the general classification of PH and of the more detailed approaches to classifying PAH-CHD is vital for clinicians managing adult patients with congenital heart disease.

**Abbreviations**

BMPR-2: Bone morphogenetic protein receptor-2; CHD: Congenital heart disease; CTEPH: Chronic thromboembolic PH; ES: Eisenmenger Syndrome; HIV: Human immunodeficiency virus; mPAP: Mean pulmonary arterial pressure; PAH: Pulmonary arterial hypertension; PH: Pulmonary hypertension; PH-LHD: PH due to left heart disease; PVDD: Pulmonary vascular disease unit; PVR: Pulmonary vascular resistance

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