4.9 Pulmonary hypertension

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1. INTRODUCTION

- Pulmonary hypertension (PH) is an "umbrella term" used for many different conditions that result in an elevation of the mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg. The five major clinical and pathophysiological groups that result in elevated pulmonary pressure are summarized in **Table 1**.
- By definition, the diagnosis of PH requires invasive measurement of the pulmonary pressure by right-heart catheterization, which, due to lack of immediate therapeutic implications, is rarely performed in patients with CF.
- In the context of CF, PH is mainly due to
  - hypoxic pulmonary vasoconstriction
  - vessel compression by air trapping
  - progressive reduction of the pulmonary capillaries as a consequence of the inflammatory destruction of the lung tissue.

  These mechanisms result in vascular remodeling of the pulmonary arteries and, as such, to chronic elevation of the pulmonary pressure.
- In addition to 'group 3' pulmonary hypertension (**Table 1**), other factors that may contribute to PH in CF include portal hypertension in patients with CF-associated liver cirrhosis ("portopulmonary hypertension") and chronic thromboembolic events. Exact data on these issues are lacking.

Table 1: Groups of Pulmonary Hypertension (Nice 2013)[1,2]

1	Pulmonary arterial hypertension – idiopathic – heritable – drug-induced – associated with: CTD,HIV, portal hypertension, congenital heart disease, schistosomiasis
1'	Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1''	Persistent pulmonary hypertension of the newborn
2	PH due to left heart disease
3	PH due to lung diseases and/or hypoxia
4	Chronic thromboembolic pulmonary hypertension (CTEPH)
5	PH with unclear multifactorial mechanisms

Abbreviations: CTEPH=chronic thromboembolic pulmonary hypertension, HIV = human immunodeficiency virus, CTD = connective tissue disease

2. EPIDEMIOLOGY AND RISK FACTORS

- Pulmonary hypertension is a common complication of end-stage CF and is reported to occur in 21-91% of patients. This wide range is due to differences in the population studied and the diagnostic method used.
- Risk factors to develop PH include
  - severe lung disease and
  - chronic pulmonary infection with *Burkholderia cepacia* complex (in particular *Burkholderia multivorans*).
- Whether the presence of PH in CF patients is associated with reduced survival is a matter of debate.

3. DIAGNOSIS

- PH in CF is probably related to disease severity of the underlying CF-lung disease.
- Echocardiography and biomarkers (i.e. NT-proBNP) are of insufficient accuracy to exclude the presence of PH in CF.
  - Despite its limitations, determination of the transtricuspid pressure gradient by echocardiography is usually used to estimate the presence of PH in CF.
  - Moreover, functional and morphological assessment of the right heart makes echocardiography an important tool in this context.
- Right-heart catheterization should be performed when out-of-proportion elevation of the pulmonary pressure (i.e. that cannot be explained by impairment of lung function and hypoxemia) is suspected. Only in these patients PH-specific therapies might be considered.
- CF patients with moderate to severe lung disease and daytime symptoms (i.e. sleepiness, morning headache, concentration difficulties) should be screened for sleep-associated hypoxemia and/ or breathing disorders that might aggravate PH **(see also Chapter "*Pulmonary disease: Clinical evaluation*")**.

4. TREATMENT

- Stabilization of lung disease to prevent further progression of pulmonary hypertension in CF patients is the primary goal.
- Long-term oxygen therapy to reduce hypoxic pulmonary vasoconstriction (indicated when pO2<7.3kPa/55mmHg or < 8kPa/60mmHg in the presence of pulmonary hypertension).
- Treatment of sleep-related hypoxemia/ breathing disorders.
- Pulmonary hypertension-specific therapies (phosphodiesterase-Inhibitors, endothelin-receptor antagonists, prostacyclin analogues) are not well studied in CF-patients.
  - Use of these therapies is discouraged excepted if PH is due to PAH co-existence.
  - Patients with severe pulmonary hypertension without severe lung disease ("out-of-proportion") might benefit from specific therapies. A trial of such therapy should be started in a center experienced for the treatment of both conditions and under close monitoring for clinical deterioration and oxygenation. Phosphodiesterase-5-Inhibitors should be the first choice in this setting.

- Lung transplantation is currently the only treatment option for end-stage lung disease in CF patients. Of note, the presence of pulmonary hypertension / right ventricular dysfunction is no contraindication for transplantation since prompt recovery is observed after lung transplantation. However, the transplant surgeon has to be informed, since elevated pulmonary pressure might be an indication for extracorporeal life support during the operation **(see also Chapter "*Transplantation*")**.

5. LITERATURE

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