Pulmonary hypertension is a severe life-limiting disease, often affecting younger patients. The connection between HIV infection and the development of pulmonary hypertension is well documented (Mette 1992, Simonneau 2004). However, the underlying pathobiology still remains unclear. Given that the prognosis of HIV infection has been improved by HAART, severe pulmonary hypertension is becoming a life-limiting factor (Nunes 2002).

**Etiology, pathogenesis, classification**

Pulmonary hypertension can be caused by vasoconstriction, reduction of arterial elasticity by structural remodeling of the vessel wall, obstruction of the vessel, and vessel rarification. All forms show the development of functional alterations (reversible vasoconstriction) and structural changes (vascular remodeling), and often occur in combination with intravasal thrombosis. The increase in right ventricular afterload induces right ventricular hypertrophy and/or dilatation.

Chronic pulmonary hypertension is classified using five groups according to the classification developed at the *World Symposium on Primary Pulmonary Hypertension* 1998 in Evian (modified in Venice 2003). HIV-associated pulmonary hypertension belongs to group number one (PAH):

**Pulmonary arterial hypertension (PAH)**

1.1 Primary pulmonary hypertension
   a) Sporadic disorder
   b) Familial disorder

1.2 Associated with
   a) Collagen vascular disease
   b) Congenital (right-left) systemic-pulmonary shunt
   c) Portal hypertension
   d) **HIV-associated pulmonary hypertension**
   e) Drugs
   f) Persisting PAH of the newborn
Pulmonary hypertension is classified into three clinical stages:

**Latent pulmonary hypertension** is characterized when mean pulmonary arterial pressures (PAP) are below 21 mmHg with an exercise-induced increase to values above 30 mmHg. The patients suffer from dyspnea upon exercise. In **manifested pulmonary hypertension**, the mean PAP exceeds 25 mmHg at rest. Patients already suffer from dyspnea on light exercise. **Severe pulmonary hypertension** is characterized by a severely reduced cardiac output at rest, which cannot be increased upon exercise, due to the increase in right ventricular afterload. Thus, patients are unable to perform any physical activity without distress.

**Diagnosis**

**Right heart catheterization**

For diagnosis of chronic pulmonary hypertension, right heart catheterization is still considered to be the gold standard. It allows the essential parameters of pulmonary hemodynamics to be evaluated. The main parameter is pulmonary resistance, which can be abnormal even without affecting pulmonary arterial pressure. A test for reversibility of vasoconstriction should be performed at the stage of manifested pulmonary hypertension, to identify patients responding to vasodilative therapy. These “responders” are identified using oxygen insufflation or vasodilators during right heart catheterization. For example, during inhalation of nitric oxide, these patients show a decrease in pulmonary arterial pressure of 30% and a simultaneous normalization of cardiac output.

**ECG**

ECG alterations induced by pulmonary hypertension are present after a two-fold increase in right heart musculature. Typical signs are:

- right axis deviation (mean QRS-axis > +110°)
- RS-ratio in lead V6 < 1
- S wave in lead I and Q wave in lead III
- S waves in lead I, II and III
- increased P-wave amplitude (not obligatory).

**Chest radiography**

Pulmonary hypertension can be inferred by chest radiography observations:

- Enlarged right descending pulmonary artery (diameter > 20 mm)
- Central pulmonary arterial dilatation in contrast to narrowed segmental arteries
- Pruning of peripheral pulmonary blood vessels
- Enlargement of transverse heart diameter and increase of retrosternal contact area of the right ventricle
Echocardiography

Echocardiography allows recognition of right ventricular dilatation and estimation of systolic pulmonary arterial pressure. Typical signs are:

- right ventricular myocardial hypertrophy
- abnormal septum movements
- abnormal systolic intervals
- abnormal movement patterns of the pulmonary valve
- altered ejection flow profile of the right ventricle (transthoracic Doppler echocardiography).

Ventilation-perfusion scan, pulmonary angiography and CT scan

These radiological techniques are used to identify or exclude chronic thromboembolic pulmonary hypertension (CTEPH) and may guide operative treatment. CTEPH is an important differential diagnosis in intravenous drug abusing HIV-patients suffering from recurring thromboembolisms (Figure 1).

Therapy

General treatment

Various modalities of general treatment have been established for the therapy of pulmonary hypertension on the basis of empirical data. These are:

1. Diuretics

In the later stages of pulmonary hypertension, volume retention may cause an enormous increase in the right ventricular preload followed by congestive hepatomegaly, edema and ascites formation. Volume retention is not only caused by chronic right heart failure but also by stimulation of the renin-angiotensin system followed by elevated aldosterone levels. For this reason, a combination of loop diuretics (e.g. furosemide 20-80 mg per day) and aldosterone antagonists (e.g. aldactone 50-200 mg per day) has proved to be successful. The usual contraindications, as well as the risk of dehydration followed by a critical decrease of right ventricular preload, have to be considered. A preload of about 6-10 mmHg is needed for optimal right ventricular performance.

2. Digitalis

The use of digitalis is still much debated. According to a randomized placebo-controlled double-blinded trial, only patients simultaneously suffering from Cor pulmonalis and decreased left ventricular function benefit from digitalis medication. However, digitalis medication is always justified in the case of tachycardic atrial arrhythmias. It has to be considered that digitalis has a high arrhythmogenic potential in combination with hypoxemia, which might lead to severe complications.
3. Anticoagulation

After considering the contraindications, the application of heparin or oral anticoagulants such as phenprocoumon and warfarin, are an established treatment for chronic pulmonary hypertension. Long-term anticoagulation therapy addresses the following aspects of the pathophysiology of PAH:

- increased risk of in-situ thrombosis caused by altered blood flow in narrowed and deformed pulmonary vessels
- increased risk of thrombosis caused by peripheral venous stasis, right ventricular dilatation and reduced physical exercise
- decreased levels of circulating thrombin and fibrinogen degradation products, which are supposed to act as growth factors in vascular remodeling processes.
The dose of anticoagulants should be adjusted to maintain the prothrombin time at an international normalized ratio (INR) of 2.5.

4. HAART
HAART is considered as a general treatment for HIV-associated pulmonary hypertension. According to the CDC classification, pulmonary hypertension is a symptomatic complication and therefore classified as category B. This is independent of CD4 cell numbers and virus load, indicating an obligation for antiretroviral treatment. Evidence shows that the prognosis of HIV-associated pulmonary hypertension is improved upon effective antiretroviral therapy (Zuber 2004). Furthermore, the immune status of this high-risk group has to be stabilized to prevent systemic infection, especially pneumonia.

Specific treatment
The aim of specific therapy is to decrease pulmonary arterial pressure, thereby reducing the right ventricular afterload. Substances that currently used for the treatment of pulmonary hypertension or tested in clinical studies are:

- Calcium channel blockers
- Prostanoids (intravenous, inhalative, oral, subcutaneous)
- Endothelin receptor antagonists (selective, none-selective)
- Phosphodiesterase-5 inhibitors

In addition to the immediate effect of muscle relaxation, some vasodilators (especially prostanoids and phosphodiesterase-5 inhibitors) seem to have a sustained antiproliferative effect.

1. Calcium channel blockers
Currently nifedipine and diltiazem are the most commonly used calcium channel blockers. Around 5-10% of primary pulmonary hypertension patients are so-called responders. The response to calcium channel blockers should be evaluated during right heart catheterization.

The major disadvantage of oral calcium channel blockers is their effects on the systemic circulation. Peripheral vasorelaxation causes hypotension and the negative inotropic effect of calcium channel blockers leads to a reduction in cardiac output. Furthermore, non-selective vasodilation in the pulmonary circulation may have disadvantageous effects on gas exchange by increasing ventilation-perfusion mismatches. For long-term therapy, up to 250 mg nifedipine or 720 mg diltiazem is used. The dose must be increased slowly over weeks to the correct treatment dosage.

2. Intravenous prostacyclin
Reduction of endothelial prostacyclin synthesis in lung tissue has been described in patients suffering from pulmonary hypertension (Christman 1992, Tuder 1999). Therefore, substitution of exogenous synthetic prostacyclin is an obvious therapeutic option. Due to its short half-life, iloprost is continuously infused intravenously using a portable pump via a catheter or an implanted port. The intravenous dosage
of iloprost is slowly increased to a usual dose of between 0.5 and 2.0 ng per kg bodyweight per minute.

The treatment of outpatients with intravenous prostacyclin is today an established treatment for long-term therapy of severe pulmonary hypertension (Barst 1996, Sitbon 2002). Long-term therapy with intravenous prostacyclin induces a sustained hemodynamic benefit in the treatment of primary pulmonary hypertension (e.g. HIV-associated pulmonary hypertension).

The disadvantages of intravenous prostacyclin are:

- systemic side effects of non-selective vasodilators, e.g. arterial hypotension, orthostasis, skin hyperemia, diarrhea, jaw- and headache
- risk of acute right heart decompensation due to application failures
- possible catheter infection
- tachyphylaxis

Tachyphylaxis is observed in long-term application of intravenous prostacyclin and requires increased doses.

**Conclusion:** experiences with prostacyclin in HIV-associated pulmonary hypertension are based on smaller, uncontrolled trials. However, these studies suggest an improvement in the prognosis of affected patients (Aguilar 2000, Cea-Calvo 2003).

### 3. Inhalative prostanoids

Many disadvantages of intravenous application can be avoided by using aerosolized prostanoids (e.g. the recently approved prostanoid Ventavis™). Alveolar deposition of prostanoids stimulates a selective intrapulmonary effect. Repeated inhalation of iloprost has proved to be effective and safe in HIV-negative patients in a recent multi-centric, randomized placebo-controlled trial (Olschewski 2002). Iloprost-treated patients showed a significant improvement in exercise capacity, as measured by a six-minute walk test, as well as in NYHA classification.

The effect of this treatment on HIV-associated pulmonary hypertension was demonstrated in a further clinical trial at our center (Ghofrani 2004). Disadvantages of this form of therapy include the sophisticated aerosolation technology, the short duration of action after a single application (60-90 min), requiring frequent inhalations (6-9 per day), and the therapy-free interval during the night. Per day, 25-75 µg iloprost are given in 6-9 inhalations.

### 4. Endothelin receptor antagonists

Several experimental trials have proved the effectiveness of selective and non-selective endothelin antagonists. A phase III trial on the orally administered endothelin antagonist bosentan showed an improvement in physical exercise capacity and an increase in complication-free survival time of PPH patients (Rubin 2002). Applied doses vary between 62.5 and 125 mg twice daily. The major side effect of this therapy is an elevation of liver enzymes. Therefore, stringent controls of liver enzymes are necessary. The use of bosentan in patients suffering from HCV/HIV co-infection has to be considered carefully.
Based on these data, bosentan was approved for the treatment of pulmonary arterial hypertension in Europe. Due to the potential increase in liver enzymes, frequent controls of liver enzymes are required. Only physicians registered by the company Actelion and admitted to the prescription list are able to prescribe bosentan. An uncontrolled study has reported initial experiences in using bosentan to treat HIV-associated pulmonary hypertension (Sitbon 2004).

5. Phosphodiesterase-5 (PDE5)-inhibitors

Sildenafil (Revatio™) was the first phosphodiesterase-5 inhibitor to be approved for the therapy of pulmonary hypertension by the FDA last year, and at the beginning of this year by the EMEA in Europe. Revatio™ is also approved for use in HIV-associated pulmonary hypertension, although combination with protease inhibitors is not recommended because of possible interactions due to the same metabolic pathway (cytochrome P450 cyp 3A).

Considering the association of the groups of pulmonary arterial hypertension (Venice 2003), a similar therapeutic regime to that used for idiopathic pulmonary hypertension can be applied, depending on the clinical severity of the disease (Figure 2). A daily dose of 25-150 mg sildenafil is usually given in two or three single applications.
Conclusion for clinicians

HIV-patients suffering from exercise-induced dyspnea should be tested for pulmonary hypertension when other pulmonary or cardiac diseases (e.g. restrictive or obstructive ventilation disorders, pneumonia, coronary heart disease) have been excluded. The incidence of pulmonary hypertension is elevated by a factor of 1,000 in HIV patients compared to the general population, excluding estimated numbers of unreported cases.

A suspected diagnosis of pulmonary hypertension can be substantiated by non-invasive diagnostic methods (e.g. echocardiography). Since new therapeutic options have recently become available, correct diagnosis is essential.

Further diagnosis and treatment of patients suffering from every kind of pulmonary hypertension should be performed in specialized centers with experience in the treatment of pulmonary hypertension and HIV infection.

References and Internet addresses


HIV-associated Pulmonary Hypertension