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MODERN PRACTICE OF INTERNAL MEDICINE WITH EMERGENCY CONDITIONS

Management of patients with pulmonary hypertension

Guidelines for students and interns

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Management of the patients with pulmonary hypertension

General Outcome

The students should be able to describe main links of pathogenesis, clinical features, diagnostic and treatment of pulmonary hypertension.

The aim of this topic is to provide the student with an opportunity to:

- Provide a basic overview of the pathophysiology, diagnosis, and classification of pulmonary hypertension.
- Evaluate guideline-based management strategies for the treatment of pulmonary hypertension.
- Develop an individualized pharmacotherapy and monitoring plan for the management of pulmonary hypertension, when given specific patient information.

Specific Learning Outcomes:

Upon successful completion of this unit, the students should be able to:

1. Describe the pulmonary hypertension classifications.
2. Describe the main mechanism of etiopathogenesis.
3. Describe the main clinical features of pulmonary hypertension.
4. List and describe the group of drugs that are used in the treatment of pulmonary hypertension and give specific examples of each.
5. Make a treatment plan of patient with pulmonary hypertension.

Specification of the theoretical question for training of "Management of the patients with pulmonary hypertension"

Student must know:

1. What is the definition of pulmonary hypertension?
2. What are the main causes of pulmonary hypertension?
3. What are the main pathogenetic links of pulmonary hypertension?
4. What are the main types of pulmonary hypertension?
5. What laboratory tests are used in patients with pulmonary hypertension?
6. What imaging studies are used in patients with pulmonary hypertension?
7. What treatment methods are used to decrease intestinal ammonia production in patients with pulmonary hypertension?
8. What treatment methods are used to increase ammonia clearance in patients with pulmonary hypertension?
9. What treatment methods are used to improve sleep disturbances in patients with pulmonary hypertension?

DEFINITIONS

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). Available data have shown that the normal PAPm at rest is 14+3 mm Hg with an upper limit of normal of approximately 20 mm Hg. The clinical significance of a PAPm between 21 and 24 mm Hg is unclear. Patients presenting with a pulmonary artery pressure (PAP) in this range should be carefully followed when they are at risk for developing PAH [e.g. patients with connective tissue disease (CTD) or family members of patients with heritable PAH (HPAH)]. Due to the lack of reliable data that define which levels of exercise-induced changes in PAPm or PVR have prognostic implications, a disease entity 'PH on exercise' can not be defined and should not be used.

A recent retrospective study has proposed a definition of PH on exercise with the combination of PAPm and total PVR data, but no outcome prospective validation has been provided. The term PAH describes a group of PH patients characterized haemodynamically by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mm Hg and a PVR . Wood units (WU) in the absence of other causes of precapillary PH such as PH due to lung diseases, CTEPH or other rare diseases. According to various combinations of PAP, PAWP, cardiac output (CO), diastolic pressure gradient (DPG) and PVR, assessed in stable clinical conditions, different haemodynamic definitions of PH are shown in *table* together with their corresponding clinical classification. The reasons for the updated definitions of post-capillary PH are reported in the specific section.

Haemodynamic definitions of pulmonary hypertension

Definition	Characteristic	Clinical group(s)
PH	PAPm ≥ 25 mmHg	All
Pre-capillary PH	PAPm ≥ 25 mmHg. PAWP ≤ 15 mmHg.	1. Pulmonary arterial hypertension. 3. PH due to lung diseases. 4. Chronic thromboembolic PH. 5. PH with unclear and/or multifactorial mechanisms.
Post-capillary PH	PAPm ≥ 25 mmHg. PAWP > 15 mmHg.	2. PH due to left heart disease. 5. PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (Ipc-PH)	DPG < 7 mmHg and/or PVR ≤ 3 WUc	
Combined post-capillary and pre-capillary PH (Cpc-PH)	DPG ≥ 7 mmHg and/or PVR > 3 WUc	

CO – cardiac output; DPG – diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP – mean pulmonary arterial pressure; PAWP – pulmonary arterial wedge pressure; PH – pulmonary hypertension; PVR – pulmonary vascular resistance; WU – Wood units.

CLASSIFICATION

The clinical classification of PH is intended to categorize multiple clinical conditions into five groups according to their similar clinical presentation, pathological findings, haemodynamic characteristics and treatment strategy. The clinical classification may be updated when new data are available on the above features or when additional clinical entities are considered.

Comprehensive clinical classification of pulmonary hypertension (updated from Simonneau et al.):

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.

1.4.2. Human immunodeficiency virus (HIV) infection.

1.4.3. Portal hypertension.

1.4.4. Congenital heart disease.

1.4.5. Schistosomiasis.

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis:

1'.1. Idiopathic.

1'.2. Heritable.

1'.2.1. EIF2AK4 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.

2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies.

2.5. Congenital /acquired pulmonary veins stenosis.

3. Pulmonary hypertension due to lung diseases 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.

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions:

4.1. Chronic thromboembolic pulmonary hypertension.

4.2. Other pulmonary artery obstructions.

4.2.1. Angiosarcoma.

4.2.2. Other intravascular tumors.

4.2.3. Arteritis.

4.2.4. Congenital pulmonary arteries stenoses.

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.

5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders.

5.4. Others: pulmonary tumoral thrombothic microangiopathy, osing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension.

ETIOPATHOGENESIS

Reporting in the literature of PH incidence data at the global level is poor. In the UK, a prevalence of 97 cases per million with a female – male ratio of 1.8 has been reported. The age-standardized death rate in the USA ranges between 4.5 and 12.3 per 100,000 population. Comparative epidemiological data on the prevalence of the different groups of PH are not widely available, but it is clear that LHD (group 2) is believed to be the most common cause of PH, although severe Phis relatively un common in this setting. Al though patients belonging to groups 2 and 3 represent an important part of the clinical practice, there is disproportionately little information about the demographics and clinical course of this segment of the PH population, suggesting that registry database methodology may be useful for these groups. Globally, schistosomiasis-associated PAH and high altitude–related PH represent an important burden to mankind.

Group 1 (PAH): Several registries have described the epidemiology of PAH.10–12. The lowest estimate of the prevalence of PAH and idiopathic PAH (IPAH) are 15 cases and 5.9 cases per million adult population, respectively. The lowest estimate of PAH incidence is 2.4 cases per million adult population per year. In Europe, PAH prevalence and incidence are in the range of 15–60 subjects per million population and 5–10 cases per million per year, respectively. In registries, around half of PAH patients have idiopathic, heritable or drug-induced PAH. In the subgroup of associated PAH conditions (APAH), the leading cause is CTD, mainly systemic sclerosis (SSc). PAH may occur in different settings depending on associated clinical conditions. IPAH corresponds to sporadic disease, without any familial history of PAH or known triggering factor. While the mean age of patients with IPAH in the first US National Institutes of Health registry created in 1981 was 36 years, PAH is now more frequently diagnosed in elderly patients, resulting in a mean age at diagnosis between 50 and 65 years in current registries. Furthermore, the female predominance is quite variable among registries and may not be present in elderly patients, and survival appears to have improved over time.

A number of risk factors for the development of PAH has been identified and are defined as any factor or condition that is suspected to play a predisposing or facilitating role in disease development. Risk factors were classified as definite, likely or possible, based on the strength of their association with PH and their probable causal role. A definite association is acknowledged in the case of either an epidemic, such as occurred with appetite suppressants, or if large, multicentre epidemiological studies demonstrate an association between the clinical condition or drug and PAH. A likely association is acknowledged if a single-centre case-control study or multiple case series demonstrate an association or if clinical and haemodynamic recovery occurs after stopping exposure, such as occurred in dasatinib-induced PAH. A possible association can be suspected, for example, for drugs with similar mechanism so faction as those in the definite or likely category but which have not yet been studied, such as drugs used to treat attention deficit disorder.

Group 2 (PH due to LHD): The prevalence of PH in patients with chronic heart failure increases with the progression of functional class (FC) impairment. Up to 60 % of patients with severe left ventricular (LV) systolic dysfunction and up to 70 % of patients with heart failure with preserved ejection fraction may present with PH. In left-sided valvular diseases, the prevalence of PH increases with the severity of the defect and of the symptoms. PH can be found in virtually all patients with severe symptomatic mitral valve disease and in up to 65 % of those with symptomatic aortic stenosis.

Group 3 (PH due to lung diseases and/or hypoxaemia): Mild PH is common in both severe interstitial lung disease and severe chronic obstructive pulmonary disease (COPD), while severe PH is uncommon. Severe PH can be seen in the combined emphysema/fibrosis syndrome, where the prevalence of PH is high.

Group 4 [CTEPH and other PA obstructions]: In the Spanish PH Registry, CTEPH prevalence and incidence were 3.2 cases per million and 0.9 cases per million per year, respectively. Even though a prevalence of CTEPH of 3.8 % has been reported in survivors of acute pulmonary embolism (PE), the true incidence of CTEPH after acute PE is lower, in the range of 0.5–2 %. A history of acute PE was reported for 74.8 % of patients from the International CTEPH Registry. Associated conditions included thrombophilic disorders (lupus anticoagulant/antiphospholipid antibodies, protein S and C deficiency, activated protein C resistance including factor V Leiden mutation, prothrombin gene mutation, antithrombin III deficiency and elevated factor VIII) in 31.9 % of patients and splenectomy in 3.4 %.

CLINICAL FEATURES

The symptoms of PH are non-specific and mainly related to progressive right ventricular (RV) dysfunction. Initial symptoms are typically induced by exertion. They include shortness of breath, fatigue, weakness, angina and syncope. Less commonly patients may also describe dry cough and exercise-induced nausea and vomiting. Symptoms at rest occur only in advanced cases. Abdominal distension and ankle oedema will develop with progressing RV failure. The presentation of PH may be modified by diseases that cause or are associated with PH as well as other concurrent diseases. In some patients the clinical presentation maybe related to mechanical complications of PH and the abnormal distribution of blood flow in the pulmonary vascular bed. These include haemoptysis related to rupture of hypertrophied bronchial arteries, as well as symptoms attributable to pulmonary arterial dilatation such as hoarseness caused by compression of the left recurrent laryngeal nerve, wheeze caused by large airway compression and angina due to myocardial ischaemia caused by compression of the left main coronary artery. Significant dilation of the PA may result in its rupture or dissection, leading to signs and symptoms of cardiac tamponade. The physical signs of PH include left parasternal lift, an accentuated pulmonary component of the second heart sound, an RV third heart sound, a pansystolic murmur of tricuspid regurgitation and a diastolic murmur of pulmonary regurgitation. Elevated jugular venous pressure, hepatomegaly, ascites, peripheral oedema and cool extremities characterize patients with advanced disease. Wheeze and crackles are usually absent.

Clinical examination may suggest an underlying cause of PH. Telangiectasia, digital ulceration and sclerodactyly are seen in scleroderma, inspiratory crackles may point towards interstitial lung disease and spider naevi, testicular atrophy, and palmar erythema suggest liver disease. When digital clubbing is encountered, PVOD, cyanotic CHD, interstitial lung disease or liver disease should be considered.

DIAGNOSTIC

Blood tests are not useful in diagnosing PH, but are required to identify the aetiology of some forms of PH as well as end organ damage. Routine biochemistry, haematology and thyroid function tests are required in all patients, as well as a number of other specific blood tests. Liver function tests may be abnormal because of high hepatic venous pressure, liver disease and/or endothelin receptor antagonist (ERA) therapy. Hepatitis serology should be performed if clinical abnormalities are noted. Thyroid disease is common in PAH and may develop during the course of the disease. This should always be considered in cases of abrupt deterioration. Serological testing is required to detect under lying CTD, hepatitis and human immunodeficiency virus (HIV). Up to 40 % of patients with IPAH have elevated antinuclear antibodies usually in a low titre (1:80).

An **electrocardiogram (ECG)** may provide supportive evidence of PH, but a normal ECG does not exclude the diagnosis. An abnormal ECG is more likely in severe rather than mild PH. ECG abnormalities may include P pulmonale, right axis deviation, RV hypertrophy, RV strain, right bundle branch block, and QTc prolongation. While RV hypertrophy has insufficient sensitivity (55 %) and specificity (70 %) to be a screening tool, RV strain is more sensitive Prolongation of the QRS complex and QTc suggest severe disease. The ECG differential diagnosis includes anterolateral myocardial ESC/ERS. In contrast to PH, ECG changes in ischaemia more commonly affect the lateral and inferior leads, and when present in the anterior chest leads are usually accompanied by a Q wave in V1 to V3, and rarely cause right axis deviation. Supraventricular arrhythmias may occur in advanced disease, in particular atrial flutter, but also atrial fibrillation, with a cumulative incidence in 25 % of patients after 5 years. Atrial arrhythmias compromise CO and almost invariably lead to further clinical deterioration. Ventricular arrhythmias are rare.

Chest radiograph In 90 % of patients with IPAH the chest radiograph is abnormal at the time of diagnosis. Findings in patients with PAH include central pulmonary arterial dilatation, which contrasts with "pruning" (loss) of the peripheral blood vessels. Right atrium (RA) and RV enlargement may be seen in more advanced cases. A chest radiograph may assist in differential diagnosis of PH by showing signs suggesting lung disease (group 3) or pulmonary venous congestion due to LHD (group 2). Chest

radiography may help in distinguishing between arterial and venous PH by respectively demonstrating in- creased and decreased artery : vein ratios.

Overall, the degree of PH in any given patient does not correlate with the extent of radiographic abnormalities. As for ECG, a normal chest radiograph does not exclude PH.

Pulmonary function tests and **arterial blood gases** identify the contribution of underlying airway or parenchymal lung disease. Patients with PAH have usually mild to moderate reduction of lung volumes related to disease severity. Although diffusion capacity can be normal in PAH, most patients have decreased lung diffusion capacity for carbon on oxide (DLCO). An abnormal low DLCO, defined as, 45 % of predicted, is associated with a poor outcome. The differential diagnosis of a low DLCO in PAH includes PVOD, PAH associated with scleroderma and parenchymal lung disease. Although airflow obstruction is unusual, peripheral airway obstruction can be detected. Due to alveolar hyperventilation at rest, arterial oxygen pressure (PaO2) remains normal or is only slightly lower than normal and arterial carbon dioxide pressure (PaCO2) is decreased. COPD as a cause of hypoxic PH is diagnosed on the evidence of irreversible airflow obstruction together with in creased residual volumes and reduced DLCO. Arterial blood gases of COPD patients show a decreased PaO2 with normal or increased PaCO2. A decrease in lung volume combined with decreased diffusion capacity for carbon on oxide may indicate interstitial lung disease.

The severity of emphysema and of interstitial lung disease can be diagnosed using high-resolution computed tomography (CT). Combined emphysema and pulmonary fibrosis may pseudonormalize spirometry, although the DLCO is almost always reduced, emphasizing then need to interpret pulmonary function alongside lung imaging. The prevalence of nocturnal hypoxaemia and central sleep apnoeas are high in PAH (70–80 %). Overnight oximetry or polysomnography should be performed where obstructive sleep apnoea syndrome or hypoventilation are considered.

Transthoracic echocardiography is used to image the effects of PH on the heart and estimate PAP from continuous wave Doppler measurements. Echocardiography should always be performed when PH is suspected and may be used to infer a diagnosis of PH in patients in whom multiple different echocardiographic measurements are consistent with this diagnosis. When treatment of PH itself is being considered, echocardiography alone is not sufficient to support a treatment decision and cardiac catheterization is required. Detailed guidelines describing the echocardiographic assessment of the right heart can be found in documents created and/or endorsed by the European Association of Cardiovascular Imaging (EACVI), a registered branch of the ESC, and the reader is referred to these for further instruction.

The estimation of systolic PAP is based on the peak tricuspid regurgitation velocity (TRV) taking into account right atrial pressure (RAP) as described by the simplified Bernoulli equation. RAP can be estimated by echocardiography based on the diameter and respiratory variation in diameter of the inferior vena cava (IVC): an IVC diameter, 2.1 cm that collapses 50% with a sniff suggests a normal RA pressure of 3 mmHg (range 0–5 mmHg), whereas an IVC diameter. 2.1 cm that collapses, 50 % with a sniff or, 20 % on quiet inspiration suggests a high RA pressure of 15 mmHg (range 10–20 mmHg). In scenarios in which the IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg (range 5–10 mmHg) may be used. The EACVI recommends such an approach rather than using a fixed value of 5 or 10 mmHg for PA systolic pressure (PASP) estimations. However, given the inaccuracies of RAP estimation and the amplification of measurement errors by using derived variables, we recommend using the continuous wave Doppler measurement of peak TRV (and not the estimated PASP) as the main variable for assigning the echocardiographic probability of PH.

When peak TRV is technically difficult to measure (trivial or mild tricuspid regurgitation) some laboratories use contrast echocardiaphy [e.g. agitated saline administered by intravenous (i.v.) injection], which may improve the Doppler signal, allowing measurement of peak TRV velocity. Unfortunately, despite the strong correlation of TRV with a tricuspid regurgitation pressure gradient, Doppler-derived pressure estimation may be inaccurate in the individual patient. In patients with severe tricuspid regurgitation, TRV maybe significantly underestimated and cannot be used to exclude PH. Overestimation may also occur. PH cannot be reliably defined by a cut-off value of TRV.

Ventilation/perfusion lung scan. A ventilation/perfusion (V/Q) lung scan should be performed in patients with PH to look for CTEPH. The V/Q scan has been the screening method of choice for CTEPH because of its higher sensitivity compared with CT pulmonary angiogram (CTPA), especially in inexperienced centres. A normal- or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90–100 % and a specificity of 9 –100 %; however, many V/Q scans are not diagnostic. While in PAH the V/Q lung scan may be normal, it may also show small peripheral unmatched and non-segmental defects in perfusion. A caveat is that unmatched perfusion defects may also be seen in other pulmonary vascular disease such as PVOD. While a V/Q scan is still recommended as the screening test of choice, ventilation scans are often replaced with either a recent chest radiograph or a recent high-resolution CT of the lungs, but such practices are not really evidence-based. Also, CT is preferred in many centres since it is more readily available. A few studies suggest that single photon emission CT, also

a nuclear medicine technique, could be superior to V/Q planar scan and CTPA, but these results need more extensive evaluation. More recently, newer techniques such as three- dimensional magnetic resonance (MR) perfusion mapping, have been demonstrated to be as sensitive as traditional perfusion scintigraphy in screening for CTEPH; MR can also be used as a radiation-free modality to assess both ventilation and perfusion in CTEPH.

High-resolution computed tomography, contrast-enhanced computed tomography, and pulmonary angiography. CT imaging is a widely available tool that can provide important in- formation on vascular, cardiac, parenchymal and mediastinal abnormalities. It may suggest the diagnosis of PH (PA or RV enlargement), identify a cause of PH such as CTEPH or lung disease, provide clues as to the form of PAH (e.g. oesophageal dilation in SSc or congenital cardiac defects such as anomalous pulmonary venous drainage) and also provide prognostic information.

Cardiac magnetic resonance imaging. CMR imaging is accurate and reproducible in the assessment of RV size, morphology and function and allows non-invasive assessment of blood flow, including stroke volume, CO, pulmonary arterial distensibility and RV mass.

Abdominal ultrasound scan. Similar to blood tests, abdominal ultrasound may be useful for identification of some of the clinical entities associated with PAH. Abdominal ultrasound may confirm but not formally exclude portal hypertension. The use of contrast agents and the addition of a colour Doppler examination may improve the accuracy of the diagnosis. Portal hypertension can be reliably confirmed or excluded by measurement of the gradient between free and occluded (wedge) hepatic vein pressure at the time of RHC.

Right heart catheterization and vasoreactivity. RHC is required to confirm the diagnosis of PAH and CTEPH, to assess the severity of haemodynamic impairment and to undertake vasoreactivity testing of the pulmonary circulation in selected patients. When performed at expert centres, these procedures have low morbidity (1.1 %) and mortality (0.055 %) rates. The threshold to perform left heart catheterization in addition to RHC should be low in patients with clinical risk factors for coronary artery disease or heart failure with preserved ejection fraction, as well as in patients with echocardiographic signs of systolic and/or diastolic LV dysfunction. Measurement of LV end- diastolic pressure is also important to avoid misclassification of patients with an elevated PAWP when this is unexpected and may be inaccurate [absence of risk factors for heart failure with preserved ejection fraction, normal left atrial (LA) size and absence of echocardiographic markers of elevated LV filling pressures]. The interpretation of invasive haemodynamics should be made in the context of the clinical

picture and imaging, in particular echocardiography. Cardiac catheterization should be performed after the completion of other investigations so that it can answer specific questions that may arise from these investigations and avoid an unnecessary procedure where an alternative diagnosis is revealed. RHC is a technically demanding procedure that requires meticulous attention to detail to obtain clinically useful information. To obtain high-quality results and to be of low risk to patients, the procedure should be limited to expert centres.

TREATMENT

The therapy for PAH patients has evolved progressively in the past decade, increasing in complexity and in evidence for efficacy. The treatment process of PAH patients cannot be considered as a mere prescription of drugs, but is characterised by a complex strategy that includes the initial evaluation of severity and the subsequent response to treatment. The current treatment strategy for PAH patients can be divided into three main steps.

The initial approach includes general measures (physical activity and supervised rehabilitation, pregnancy, birth control and post-menopausal hormonal therapy, elective surgery, infection prevention, psychosocial support, adherence to treatments, genetic counselling and travel), supportive therapy (oral anticoagulants, diuretics, O2, digoxin), referral to expert centres and acute vasoreactivity testing for the indication of chronic CCB therapy.

The second step includes initial therapy with high-dose CCB in vasoreactive patients or drugs approved for PAH in non-vasoreactive patients according to the prognostic risk of the patient and the grade of recommendation and level of evidence for each individual compound or combination of compounds.

The third part is related to the response to the initial treatment strategy; in the case of an inadequate response, the role of combinations of approved drugs and lung transplantation are proposed.

General measures

Patients with PAH require sensible advice about general activities of daily living and need to adapt to the uncertainty associated with a serious chronic life-threatening disease. The diagnosis usually confers a degree of social isolation. Encouraging patients and their family members to join patient support groups can have positive effects on coping, confidence and outlook.

Supportive therapy

Oral anticoagulants. There is a high prevalence of vascular thrombotic lesions at post mortem examination in patients with IPAH. Abnormalities in coagulation and fibrinolytic pathways have also been reported. This, together with the non-specific increased risk factors for venous thromboembolism, including heart failure and immobility, represents the rationale

for oral anticoagulation in PAH. Evidence in favour of oral anticoagulation is confined to patients with IPAH, HPAH and PAH due to anorexigens and is generally retrospective and based on single-centre experience. Registry and RCT data appear to be heterogeneous and inconclusive. The potential benefits of oral anticoagulation in APAH is even less clear. Generally patients with PAH receiving therapy with long-term i.v. prostaglandins are anticoagulated in the absence of contraindications due in part to the additional risk of catheter-associated thrombosis. The role of the new oral anticoagulants in PAH is unknown. Additional information on APAH is provided in the individual chapters.

Diuretics. Decompensated right heart failure leads to fluid retention, raised central venous pressure, hepatic congestion, ascites and peripheral oedema. Although there are no RCTs on the use of diuretics in PAH, clinical experience shows clear symptomatic benefit in fluid overloaded patients treated with this therapy. The choice and dose of diuretic therapy may be left to the PAH physician. The addition of aldosterone antagonists should also be considered together with systematic assessments of electrolyte plasma levels. It is important with diuretic use to monitor renal function and blood biochemistry in patients to avoid hypokalaemia and the effects of decreased intravascular volume leading to pre-renal failure.

Oxygen. Although O2-administration has been demonstrated to reduce the PVR in patients with PAH, there are no randomised data to suggest that long-term O2-therapy is beneficial. Most patients with PAH, except those with CHD and pulmonary-to-systemic shunts, have minor degrees of arterial hypoxaemia at rest unless they have a patent foramen ovale. There are data showing that nocturnal O2-therapy does not modify the natural history of advanced Eisenmenger syndrome. Guidance may be based on evidence in patients with COPD; when arterial blood O2-pressure is consistently, <8 kPa (60 mmHg; alternatively, < 91 % of arterial O2-saturation) patients are advised to take O2 to achieve an arterial blood O2-pressure > 8 kPa. Ambulatory O2 may be considered when there is evidence of symptomatic benefit and correctable desaturation on exercise.

Digoxin and other cardiovascular drugs. Digoxin has been shown to improve CO acutely in IPAH, although its efficacy is unknown when administered chronically. It may be given to slow ventricular rate in patients with PAH who develop atrial tachyarrhythmias. No convincing data are available on the usefulness and safety of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers or ivabradine in patients with PAH.

Anaemia and iron status. Iron deficiency is common in patients with PAH and has been reported in 43 % of patients with IPAH, 46 % of pa-

tients with SSc-PAH and 56 % of patients with Eisenmenger syndrome. In all of these entities, preliminary data indicate that iron deficiency may be associated with reduced exercise capacity, and perhaps also with a higher mortality, independent of the presence or severity of anaemia. Based on these data, regular monitoring of the iron status should be considered inpatients with PAH and detection of an iron deficiency should trigger a search for potential reasons. Iron substitution should be considered in patients with iron deficiency. Some studies suggest that oral iron absorption is impaired in patients with PAH, so i.v. iron administration may be preferable.

Specific drug therapy

Calcium channel blockers. It has been increasingly recognised that only a small number of patients with IPAH who demonstrate a favourable response to acute vasodilator testing at the time of RHC do well with CCBs. The CCBs that have been predominantly used in reported studies are nifedipine, diltiazem and amlodipine, with particular emphasis on nifedipine and diltiazem. The choice of CCB is based on the patient's heart rate at baseline, with a relative bradycardia favouring nifedipine and amlodipinean darelative and a relative tachycardia favouring diltiazem. The daily doses of these drugs that have shown efficacy in IPAH are relatively high: 120–240 mg for nifedipine, 240–720 mg for diltiazem and up to 20 mg for amlodipine. It is advisable to start with an initial lower dose, e.g. 30 mg of slow release nifedipine twice a day or 60 mg of diltiazem three times a day (t.i.d.) or 2.5 mg of amlodipine once a day, and increase cautiously and progressively to the maximum tolerated dose. Limiting factors for dose increase are usually systemic hypotension and lower limb peripheral oedema. Patients with IPAH who meet the criteria for a positive vasodilator response and are treated with CCBs should be followed closely for reasons of both safety and efficacy, with a complete reassessment after 3–4 months of therapy including RHC. If the patient does not show an adequate response, defined as being in WHO-FC I or II and with a marked haemodynamic improvement (near normalization), additional PAH therapy should be instituted. In some cases the combination of CCB with the approved PAH drugs is required because of further clinical deterioration in case of CCB withdrawal attempts. Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on CCBs because of potential severe side effects (e.g. hypotension, syncope and RV failure). Vasodilator responsiveness does not appear to predict a favour-ablelong-termresponseto CCB therapy in patients with PAH in the setting of CTD, HIV, porto-pulmonary hypertension (PoPH) and PVOD.

Endothelin receptor antagonists. Activation of the endothelin system has been demonstrated in both plasma and lung tissue of PAH patients. Although it is unclear if the increases in endothelin-1 plasma levels are

a cause or a consequence of PH, these data support a prominent role for the endothelin system in the pathogenesis of PAH. Endothelin-1 exerts vasoconstrictor and mitogenic effects by binding to two distinct receptor isoforms in the pulmonary vascular smooth muscle cells, endothelin receptors type A and B.

Ambrisentan. Ambrisentan is an ERA that preferentially binds with endothelin receptor type A. Ambrisentan has been evaluated in a pilot study and in two large RCTs that have demonstrated efficacy on symptoms, exercise capacity, haemodynamics and time to clinical worsening of patients with IPAH and PAH associated with CTD and HIV infection. The incidence of abnormal liver function tests ranges from 0.8 to 3 %. Monthly liver function assessment is not mandated in the USA. An increased incidence of peripheral oedema has been reported with ambrisentan use.

Bosentan. Bosentan is an oral active dual endothelin receptor type A and B antagonist and the first molecule of its class to be synthesized. Bosentan has been evaluated in PAH (idiopathic, associated with CTD and Eisenmenger syndrome), which showed improvement in exercise capacity, FC, haemodynamics, echocardiographic and Doppler variables and time to clinical worsening. Increases in hepatic aminotransferases occurred in approximately 10 % of the patients and were found to be dose dependent and reversible after dose reduction or discontinuation. For these reasons, liver function testing should be performed monthly in patients receiving bosentan.

Macitentan. The dual ERA macitentan has been evaluated in an event-driven RCT: 742 PAH patients were treated with 3 or 10 mg macitentan as compared with placebo for an average of 100 weeks. The primary endpoint was the time from the initiation of treatment to the first occurrence of a composite endpoint of death, atrial septostomy, lung transplantation, initiation of treatment with i.v. or subcutaneous prostanoids or worsening of PAH. Macitentan significantly reduced this composite endpoint of morbidity and mortality among patients with PAH and also increased exercise capacity. Benefits were shown both for patients who had not received treatment previously and for those receiving additional therapy for PAH. While no liver toxicity was shown, reduction in blood haemoglobin $\leq$8 g/dl was observed in 4.3 % of patients receiving 10 mg of macitentan.

Phosphodiesterase type 5 inhibitors and guanylate cyclase stimulators. Inhibition of the cyclic guanosine monophosphate (cGMP) degrading enzyme phosphodiesterase type 5 results in vasodilation through the NO/cGMP pathway at sites expressing this enzyme. Since the pulmonary vasculature contains substantial amounts of phosphodiesterase type 5, the potential clinical benefit of phosphodiesterase type 5 inhibitors (PDE-5is) has been investigated in PAH. In addition, PDE-5is exert antiproliferative effects. All

three PDE-5is approved for the treatment of erectile dysfunction – sildenafil, tadalafil and vardenafil – cause significant pulmonary vasodilation, with maximum effects observed after 60, 75–90 and 40–45 minutes, respectively.

Sildenafil is an orally active, potent and selective inhibitor of phosphodiesterase type 5. Four RCTs in PAH patients treated with sildenafil have confirmed favourable results on exercise capacity, symptoms and/or haemodynamics. An RCT addressing the effects of adding sildenafil to epoprostenol showed improvements after 12 weeks in 6MWD and time to clinical worsening. Of note, seven deaths occurred in this trial, all in the placebo group. The approved dose of sildenafil is 20 mg t.i.d. Most side effects of sildenafil are mild to moderate and mainly related to vasodilation (headache, flushing, epistaxis). Based on pharmacokinetic data, an i.v. formulation of sildenafil has been proposed as a bridge for PAH patients on long-term oral treatment who are temporarily unable to ingest tablets.

Tadalafil is a once-daily dispensed selective PDE-5i. An RCT in 406 PAH patients (53 % on background bosentan therapy) treated with tadalafil 2.5, 10, 20 or 40 mg once daily has shown favourable results on exercise capacity, symptoms, haemodynamics and time to clinical worsening at the highest dose. The side-effect profile was similar to that of sildenafil.

Vardenafil is a twice-daily dispensed PDE-5i. An RCT in 66 treatment-naive PAH patients treated with vardenafil 5 mg twice daily has shown favourable results on exercise capacity, haemodynamics and time to clinical worsening. The side-effect profile was similar to that of sildenafil.

Prostacyclin analogues and prostacyclin receptor agonists. Prostacyclin is produced predominantly by endothelial cells and induces potent vasodilation of all vascular beds. This compound is the most potent endogenous inhibitor of platelet aggregation and also appears to have both cytoprotective and antiproliferative activities. Dysregulation of the prostacyclin metabolic pathways has been shown in patients with PAH as assessed by a reduction of prostacyclin synthase expression in the pulmonary arteries and of prostacyclin urinary metabolites. The clinical use of prostacyclin in patients with PAH has been extended by the synthesis of stable analogues that possess different pharmacokinetic properties but share qualitatively similar pharmacodynamic effects.

Beraprost is the first chemically stable and orally active prostacyclin analogue. An RCT in Europe and a second in the USA have shown an improvement in exercise capacity that persists up to 3–6 months. There were no haemodynamic improvements or long-term outcome benefits. The most frequent adverse events were headache, flushing, jaw pain and diarrhoea.

Epoprostenol (synthetic prostacyclin) has a short half-life (3–5 minutes) and is stable at room temperature for only 8 hours; it requires cooling

and continuous administration by means of an infusion pump and a permanent tunnelled catheter. Epoprostenol improves symptoms, exercise capacity and haemodynamics in both clinical conditions and is the only treatment shown to reduce mortality in IPAH in a single RCT study. The meta-analysis for total mortality of the three epoprostenol RCTs has shown a risk reduction for mortality of about 70 %. Long-term persistence of efficacy has also been shown in IPAH as well as in other APAH conditions and in non-operable CTEPH.

Treatment with epoprostenol is initiated at a dose of 2–4 ng/kg/min, with doses increasing at a rate limited by side effects (flushing, headache, diarrhoea, leg pain). The optimal dose varies between individual patients, ranging in the majority between 20 and 40 ng/kg/min.

Serious adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction and sepsis. Guidelines for the prevention of central venous catheter bloodstream infections have been proposed. Abrupt interruption of the epoprostenol infusion should be avoided, because in some patients this may lead to a PH rebound with symptomatic deterioration and even death. A thermostable formulation of epoprostenol is also available and does not usually require cooling packs to maintain stability beyond 8–12 hours.

Iloprost is a chemically stable prostacyclin analogue available for i.v., oral or aerosol administration. Inhaled iloprost has been evaluated in one RCT in which daily repetitive iloprost inhalations (six to nine times, 2.5–5 mg/inhalation, median 30 mg daily) were compared with placebo inhalation in patients with PAH and CTEPH. Overall, inhaled iloprost was well tolerated, with flushing and jaw pain being the most frequent side effects. Continuous i.v. administration of iloprost appeared to be as effective as epoprostenol in a small series of patients with PAH and CTEPH.232 The effects of oral iloprost have not been assessed in PAH.

Treprostinil is a tricyclic benzidine analogue of epoprostenol, with sufficient chemical stability to be administered at ambient temperature. These characteristics allow administration of the compound by i.v. and subcutaneous routes. The subcutaneous administration of treprostinil can be accomplished by a micro-infusion pump and a small subcutaneous catheter. The effects of treprostinil in PAH were assessed in an RCT and showed improvements in exercise capacity, haemodynamics and symptoms. The greatest exercise improvement was observed in patients who were more compromised at baseline and in subjects who could tolerate the upper quartile dose (>13.8 ng/kg/min). Infusion site pain was the most common adverse effect of treprostinil, leading to discontinuation of the treatment in 8 % of cases on active drug and limiting dose increases in an additional pro-

portion of patients. Treatment with subcutaneous treprostinil is initiated at a dose of 1–2 ng/kg/ min, with doses increasing at a rate limited by side effects (local site pain, flushing, headache). The optimal dose varies between individual patients, ranging in the majority between 20 and 80 ng/kg/min.

Oral treprostinil has been evaluated in two RCTs in PAH patients on background therapy with bosentan and/or sildenafil and in both trials the primary endpoint 6MWD did not reach statistical significance.

Selexipag is an orally available, selective prostacyclin IP receptor agonist. Although selexipag and its metabolite have modes of action similar to that of endogenous prostacyclin (IP receptor agonism), they are chemically distinct from prostacyclin with a different pharmacology. In a pilot RCT in PAH patients (receiving stable ERA and/or PDE-5i therapy), selexipag reduced PVR after 17 weeks. An event-driven phase 3 RCT that enrolled 1 156 patients has shown that selexipag alone or on top of mono- or double therapy with ERAs and/or PDE-5i was able to reduce by 39 % (hazard ratio 0.61, $P<0.0001$) a composite morbidity and mortality endpoint (including death from all causes, hospitalization for worsening of PAH, worsening of PAH resulting in the need for lung transplantation or atrial septostomy, initiation of parenteral prostanoids or chronic O2 for worsening of PAH and disease progression).

Навчальне видання

СУЧАСНА ПРАКТИКА ВНУТРІШНЬОЇ МЕДИЦИНИ З НЕВІДКЛАДНИМИ СТАНАМИ

Ведення хворого з легеневою гіпертензією

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