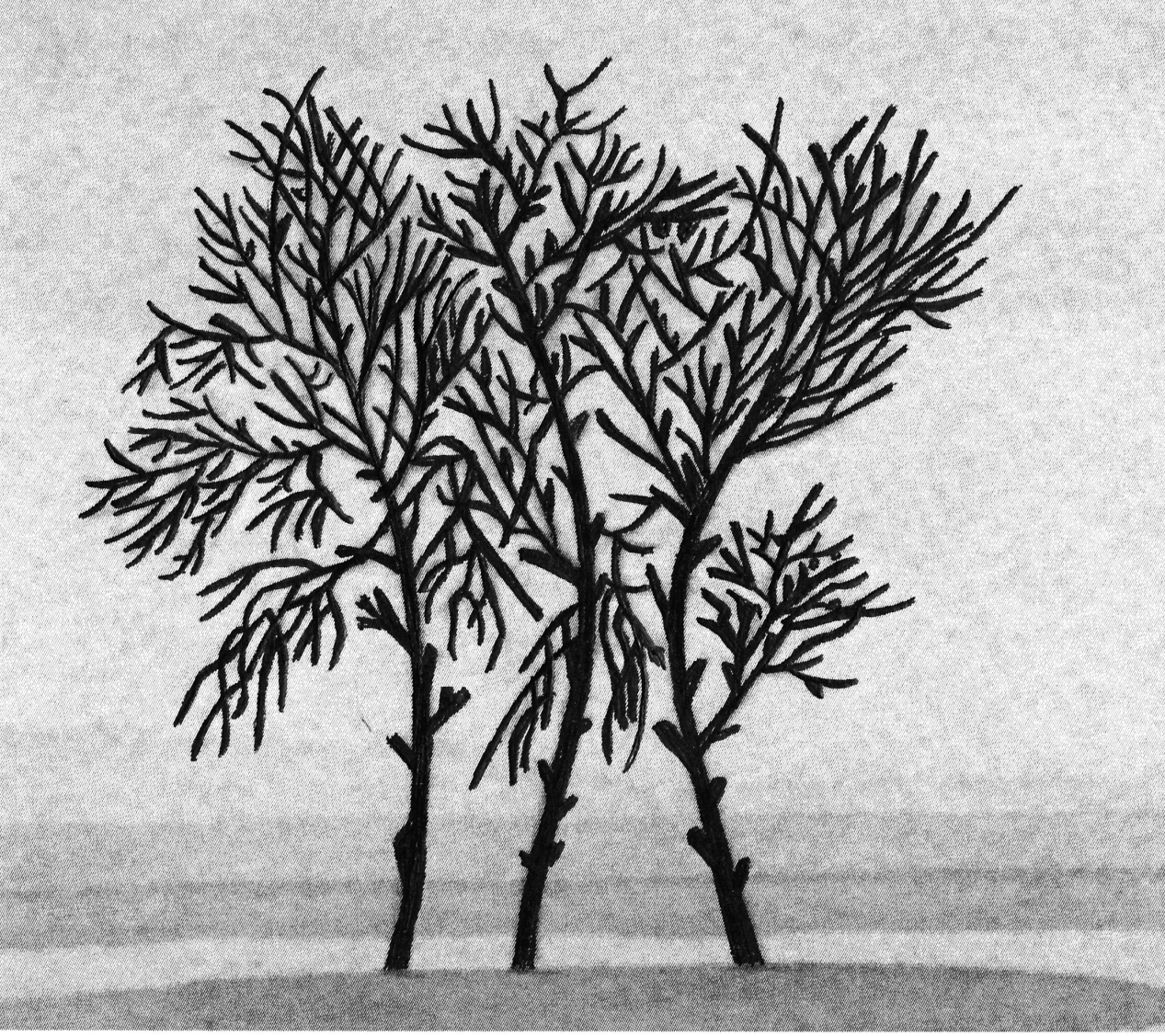

Part I

RIGHT VENTRICULAR MECHANICS IN PULMONARY HYPERTENSION

Chapter 2

DIAGNOSIS AND TREATMENT OF PULMONARY HYPERTENSION

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INTRODUCTION

Pulmonary hypertension (PH) is a descriptive name for abnormally elevated pressures in the pulmonary vasculature. PH has been defined as a mean pulmonary arterial pressure (mPAP) ≥25mm Hg at rest, measured by right heart catheterisation (RHC).[1] It can be caused by an increase in pulmonary vascular resistance (PVR), pulmonary blood flow, pulmonary venous pressure or a combination of these factors. PH leads to right ventricular (RV) overload and finally RV failure and death.[2] Commonly, PH is diagnosed at a late stage of the disease, and is associated with poor survival.[3] This underscores the importance of early recognition and treatment of PH in order to improve the outcome in this patient population.[4]

PH is characterized by different pathological lesions in the pulmonary vasculature, depending on the underlying cause. The 5th World Symposium on PH in Nice in 2013 classified PH according to these underlying aetiologies, creating five groups: (1) pulmonary arterial hypertension (PAH); (2) PH due to left sided disease; (3) PH due to lung disease; (4) chronic thromboembolic PH (CTEPH); (5) PH with unclear or multifactorial mechanisms (table 1).[5]

CLINICAL CLASSIFICATION

Group 1: Pulmonary arterial hypertension

PAH is characterized by intrinsic pathological changes in the afferent and capillary pulmonary vasculature that are not present in the other PH groups. These changes involve remodelling of the pulmonary vasculature, with thickening of the media and pronounced hyperplasia of the intima. This leads to loss of vascular lumen and distensibility, resulting in an increase in PVR[6] (>3 Wood units or >240 dynes*s*cm^{-5}) (figure 1, group 1).

PAH comprises different forms that share similar clinical and pathological characteristics (table 1). **Idiopathic PAH** is a rare form of PH where there is no family history of PAH or no associated risk factors. The prevalence is approximately 6 per million.[7] In **heritable PAH** germline mutations in the bone morphogenetic protein receptor type 2 (*BMPR2*) gene can be found in up to 75% of the cases.[5,8] Other more rare forms of heritable PAH include mutations in activin receptor-like kinase type 1 (ALK1), endoglin, bone morphogenetic protein-responsive gene *SMAD9*, caveolin-1 (CAV1), and potassium channel KCNK3.[5,8] The inclusion of heritable PAH in the clinical classification does not mandate genetic testing in all patients with PAH. A number of drugs and toxins have been associated with **drug and toxin induced PAH,** including certain weight reducing agents such as fenfluramine. In the updated classification of 2013 the use of serotonin reuptake inhibitors during pregnancy has been identified as a risk factor for the development of persistent PH of the newborn.[5]

Several diseases have been associated with PAH, including connective tissue disease, HIV infection, portal hypertension, congenital heart disease, and schistosomiasis.[5]

PAH is a fatal condition with a reported median survival of 2.8 years if the patient is not treated with PAH specific drugs.[2] Following the introduction of PAH specific drug therapy, the prognosis of PAH has improved considerably, with 1, 3, and 5 year survival rates of 85%, 68%, and 57%, respectively.[9]

Group 2: PH due to left sided heart disease

The second group comprises patients with PH caused by left sided heart failure, usually valvular disease or left ventricular (LV) failure (either diastolic or systolic). Recently, congenital or acquired

Table 1. Clinical classification of pulmonary hypertension (Nice, 2013)

Pulmonary arterial hypertension (PAH)
1.1 Idiopathic
1.2.1 Heritable: *BMPR2*
1.2.2 Heritable: ALK1, endoglin, SMAD9, CAV1, KCNK3
1.2.3 Heritable: unknown
1.3 Drugs and toxins induced
1.4 Associated with (APAH)
Connective tissue disease
HIV infection
Portal hypertension
Congenital heart disease
Schistosomiasis
1' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1'' Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3 Pulmonary hypertension due to lung disease and/or hypoxaemia
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 abnormalities
4 Chronic thromboembolic pulmonary hypertension
5 Pulmonary hypertension with unclear and/or multifactorial mechanisms
5.1 Haematological disorders: myeloproliferative disorders, splenectomy, chronic haemolytic anaemia
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumour obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

left heart inflow/outflow obstructive lesions and congenital cardiomyopathies have been added to this group.[5] The mPAP is ≥25 mm Hg and the pulmonary capillary wedge pressure (PCWP) is >15 mm Hg (figure 1, group 2).[1] PH in left sided heart disease is caused by a chronic increase in left atrial pressure, resulting in a passive increase in the PVR. The transpulmonary gradient (TPG) is usually normal or slightly elevated, except in patients with longstanding elevated left sided pressures (pulmonary venous congestion), that cause irreversible changes to the pulmonary vasculature. In such cases the TPG is >12 mm Hg and one speaks of out of proportion PH, indicating a degree of PH that cannot be explained by the severity of the underlying disease. A new proposed definition for PH due to left heart disease is isolated post-capillary PH (PCWP >15 mm Hg and diastolic PAP – PCWP <7 mm Hg) and combined post-capillary and pre-capillary PH (PCWP >15 mm Hg and diastolic

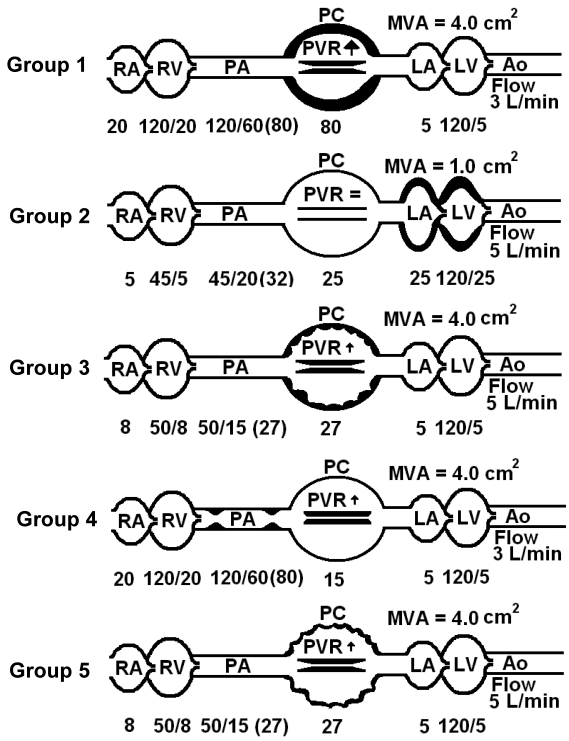

Figure 1. The basis for the classification of PH according to the World Health Organization. This figure shows the location of the problem in the pulmonary circulation that is responsible for the elevated pulmonary pressures. In addition, it demonstrates which pressures can be found in the right atrium (RA), right ventricle (RV), pulmonary artery (PA), pulmonary circulation (PC), left atrium (LA), left venctricle (LV), and aorta (Ao). It also indicates whether the pulmonary vascular resistance (PVR) is increased and what the size of the mitral valve surface (MVA) is. Groups 1–5 represent the five groups according to the pulmonary hypertension clinical classification as can be found in table 1 and in the text. Reproduced with permission from Vliegen *et al*. [39]

PAP – PCWP ≥7 mm Hg).[10] Left sided heart disease is one of the most common causes of PH with a prevalence of 68–78% in systolic heart failure patients and 85% in patients with diastolic heart failure.[11,12] The presence of PH in these patient populations is associated with increased morbidity and mortality.[11]

Group 3: PH due to lung disease

Group 3 comprises patients with chronic lung disease, including chronic obstructive lung disease (COPD) and interstitial lung disease (ILD),[5,13] and is one of the most common forms in the PH classification. The most important factor leading to an increase in PVR in patients with lung disease is chronic hypoxia (figure 1, group 3). There is a physiological ventilation–perfusion mismatch, excessive vasoconstriction, and in some cases an additional loss of pulmonary vasculature. In the long term, chronic hypoxia induces remodelling of the pulmonary vasculature, including muscularisation of the pulmonary arterioles and changes in the intima. Although the exact prevalence of PH in mild

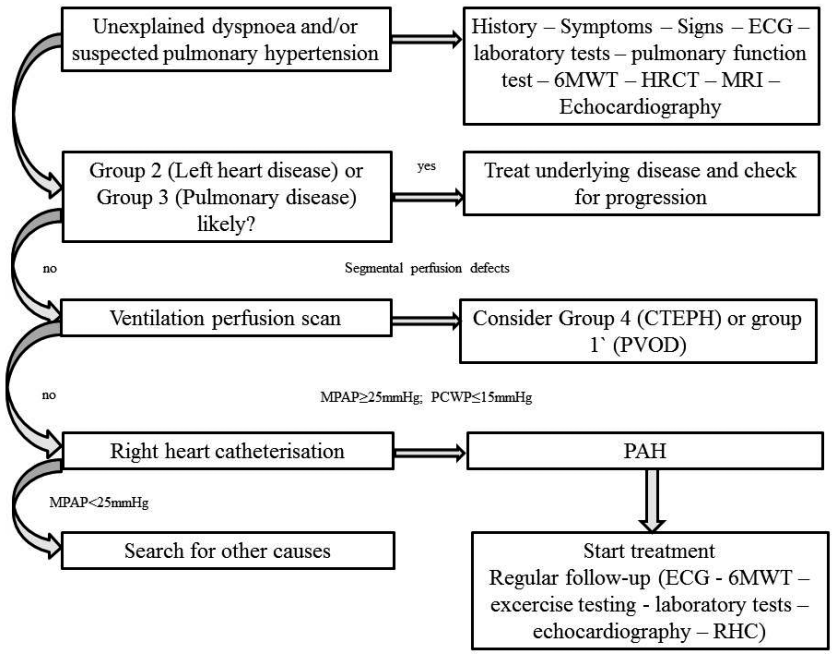

Figure 2. Flow chart of the work-up of patients with unexplained dyspnoea and/or suspected pulmonary hypertension following the recommendation in the guidelines for the diagnosis and treatment of pulmonary hypertension.[1] 6MWT, 6 min walk test; CTEPH, chronic thromboembolic pulmonary hypertension; Group, clinical group according to the pulmonary hypertension classification; HRCT, high resolution CT; MPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVOD, pulmonary veno-occlusive disease; RHC, right heart catheterisation.

to moderate COPD and ILD patients is unknown, it has been estimated that between 30–70% of COPD patients and 8–84% of ILD patients have PH.[14] Patients in group 3 tend to have a mild PH with an mPAP <30 mm Hg, but a small subgroup (<10%) has a severe PH with an mPAP >35–40 mm Hg or mPAP ≥25 mm Hg with a low cardiac index <2 L/min/m^2.[12,13] Group 3 patients have a poor prognosis, with a 5 year survival rate of 36% in COPD patients with PH.[15] The incidence and prevalence of PH due to left heart disease or lung disease is higher than that of the other PH groups. It is therefore important to demonstrate or exclude left heart disease or lung disease in patients with PH.

Group 4: Chronic thromboembolic PH

In group 4, PH is caused by a substantial loss of pulmonary arterial vascular lumen because of non-resolving pulmonary thromboembolism (figure 1, group 4). There are often intrinsic abnormalities in the coagulation cascade present, which lead to the inability to break down the blood clots. In situ thrombosis may lead to progressive obliteration of the pulmonary arterial vasculature. From a therapeutic viewpoint there is a difference between macro- and microvascular CTEPH, since macrovascular CTEPH can be cured surgically by pulmonary endarterectomy. Importantly, a large proportion (~40%) of CTEPH patients had no evident episodes of acute pulmonary embolism before diagnosis.[12]

Group 5: PH with unclear/multifactorial mechanisms

Group 5 comprises patients with disorders that lead to PH by compression, destruction of lung tissue or other extravascular destruction. This group includes haematological, systemic and metabolic disorders. In the updated clinical classification of 2013, chronic haemolytic anaemia and segmental PH have been included in this group.[5]

DIAGNOSIS

Patients with PH often present with non-specific complaints of dyspnoea, fatigue, chest pain, syncope, peripheral oedema, and palpitations, which explains why the diagnosis is often delayed. In a registry of 2967 PAH patients, 21.1% experienced symptoms >2 years before PAH was recognized.[4] Dyspnoea is caused by a restricted maximal cardiac ouput that leads to an anaerobic threshold that is lower than normal. Patients with severe PH often experience fatigue because of the low cardiac reserve.[16,17] Chest pain may be caused by a mismatch between the perfusion of the coronary arteries and the RV pressure.[18] This mismatch can be caused by coronary artery disease or excessive RV hypertrophy, but it can also be caused by RV failure resulting in a reduced preload of the LV and inadequate systemic blood pressure. Syncope can usually be attributed to arrhythmias or excessive exercise, resulting in a high heart rate with insufficient cardiac output. Figure 2 presents a flowchart of the work-up of patients with unexplained dyspnoea and/or suspected PH.

General workup

In order to evaluate the exercise tolerance, the severity of the disease and the prognosis, a 6 min walk test should be performed in every patient. This simple and standardized test is particularly useful during follow-up and has been applied in many clinical trials involving PH patients. In addition to the 6 min walk test, a cardiopulmonary exercise test can be used to assess functional capacity. In PH, a reduction in peak VO_2, arterial blood oxygen saturation and anaerobic threshold may be observed. Furthermore, an increase in the slope of the minute ventilation to carbon dioxide production ratio and dead space to tidal volume ratio may be seen, indicating impaired ventilator and pulmonary vascular function.[19] A chest x-ray provides information about lung tissue, heart size, the size of the proximal pulmonary arteries, and congestion. Also, blood tests (biochemistry, haematology and thyroid function) should be performed in every patient. It is important to screen for hypoxia (by blood gas analysis), N-terminal pro B-type natriuretic peptide (NT-proBNP) (as an indicator for left and right heart failure), underlying connective tissue disease, HIV, hepatitis, and coagulopathies, when indicated. A lung function test should be performed to assess the presence of hypoxic induced PH and to detect respiratory disease. The measurement of lung volumes and performing spirometry is important to detect respiratory disease. Another important parameter is the diffusing capacity, which is a measure of alveolar gas exchange.[1,20]

ECG

An ECG is required in all patients with suspected PH, and can be used during screening and follow-up. Figure 3 shows an ECG of a patient with severe PH. The ECG is also useful in the diagnosis of left sided heart disease, such as LV hypertrophy. Patients with PH are usually in sinus rhythm.[21]

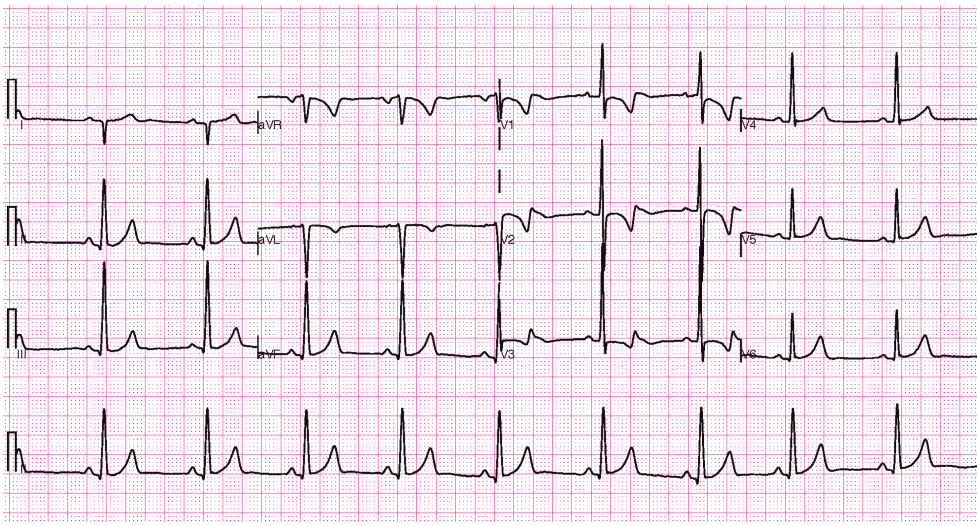

Figure 3. An ECG of a patient with PH. Note the right QRS axis, reflected by the negative QRS complex in lead I. Right ventricular hypertrophy is reflected by the large R wave in lead V1 and V2 with strain pattern in these leads. The heart rate is only 60 beats/min which is low in PH patients, and reflects a relatively favourable prognosis.

Supraventricular arrhythmias are often present in right sided pressure and/or volume overload, but generally occur at a later stage of the disease. Nevertheless, a high heart rate at rest is common, and related to the severity of the pulmonary pressure. When RV hypertrophy is present, increasing electrical forces from the right side will result in a vertical or even right heart axis. However, in mild RV pressure overload there may be no apparent changes to the QRS axis. An increased RV mass is reflected by higher R waves in V1, V2, I, II, III and aVF, and deeper S waves in I, aVL, and V3–V6. The T axis is partly dependent on the QRS axis,[22] and when right pressure overload is present, analysis of the ST-T segment may be helpful. A discordant repolarisation pattern may be an expression of RV strain or ischaemia, especially when this is present in leads V1, V2, II, III and aVF. Intra-atrial conduction is usually within normal limits. However, a conduction delay or block over the right bundle branch can manifest when the RV dilates because of chronic pressure overload. An increased P amplitude >0.25 mV in lead II can be detected as a result of severe pressure and/or volume overload in PH.[23] Although this is sensitive for elevated right sided pressures with atrial overload, a normal P wave does not exclude high pulmonary pressures. ECG parameters reflecting abnormalities in the RV in PH patients are associated with poor survival and may be useful in the therapeutic management of these patients.[23]

Imaging

Imaging is important in the initial confirmation of elevated right sided pressures, as well as for establishing the underlying aetiology. Cardiac magnetic resonance imaging (CMR) is the gold standard in the assessment of RV volumes, morphology, and function. CMR is also useful in the non-invasive evaluation of haemodynamics. Increased RV volumes accompanied by impaired LV filling

and decreased stroke volume are markers of severe PH and portend a poor prognosis.[24] Therefore, CMR provides an excellent tool in the initial evaluation of the severity of the disease as well as during follow-up. Both CT angiography and high-resolution CT enable characterization of the pulmonary vasculature and lung parenchyma. In addition, CT may also provide more insight regarding the underlying cause of PH. Dilatation of the main pulmonary artery on CT indicates the presence of PH. High-resolution CT can be used to demonstrate ILD or emphysema.[1,20] Pulmonary veno-occlusive disease is characterized on CT by central ground-glass opacifications, thickened septal lines and pleural effusion.[25] A ventilation–perfusion scan is recommended for diagnosing CTEPH. Although CT angiography may also be useful for evaluating this condition, ventilation–perfusion scanning is more sensitive and the preferred method in screening for CTEPH.[26] However, other causes of PH may also cause mismatched perfusion defects, such as pulmonary veno-occlusive disease.[27] Pulmonary angiography is the standard diagnostic tool for evaluating the operability of patients with CTEPH.

Echocardiography

Echocardiography plays an important role in the diagnosis of PH as it is the most widely available imaging test. The systolic PAP (SPAP) can be estimated by calculating the systolic pressure gradient between the RV and right atrium by the maximum velocity of the tricuspid regurgitant (TR) jet, using the modified Bernoulli equation, and adding the right atrial pressure (figure 4A).[28] Usually there is no large under- or overestimation of the SPAP, but in individual cases there can be large differences. These variations have been taken into account in the recent guidelines. The guidelines define the presence of PH, based on echocardiographic measurements, as: unlikely when the velocity of TR jet is ≤2.8 m/s or the estimated SPAP is ≤36 mm Hg; possible if the TR jet is between 2.9–3.4 ms/s (SPAP 37–50 mm Hg) or if there are other signs of PH such as RV dilatation and hypertrophy; and very likely if the TR jet is >3.4 ms/s (SPAP >50 mm Hg).[1,29] Alternatively, the end-diastolic velocity of the pulmonary regurgitation jet can be measured, which estimates the diastolic PAP, or the maximal velocity of the PR jet, which estimates the mPAP.[29] Using pulsed wave Doppler signals, the acceleration time (AT) of the RV outflow tract can also be measured. An AT <120 ms is considered pathological and corresponds to elevated pulmonary pressures.[30]

Echocardiography can also be used to assess other characteristics of PH. One of these characteristics is an abnormal motion of the interventricular septum in the direction of the LV during systole. This can be recognised on echocardiography by the D-shape of the LV. The degree of this systolic flattening of the interventricular septum can be expressed by the eccentricity index, where a normal value is 1 and in the case of increased RV pressure >1 (figure 4B).[29] Chronic elevated pulmonary pressures may also lead to RV hypertrophy, dilatation and dysfunction, and can be evaluated by echocardiography, but are usually seen at a later stage of the disease (figure 4C).[29] RV function is one of the main determinants of the long term outcome in PH. However, the accuracy of RV function assessed by echocardiography may be reduced because of the complex anatomy of the RV. There are several measurements available that correlate to RV ejection fraction and may be used in the evaluation of PH. Tricuspid annular plane systolic excursion (TAPSE) measures the systolic movement of the tricuspid annulus, using M-mode (figure 4D). Other parameters that have demonstrated clinical utility and value for RV function are the Tei index, fractional area change,

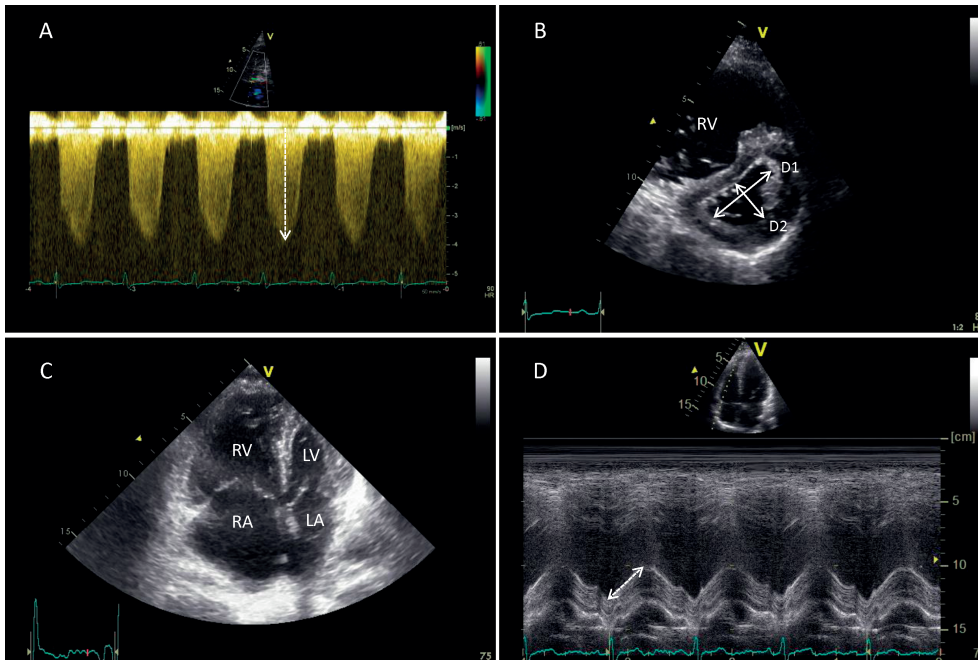

Figure 4. Echocardiographic signs of pulmonary hypertension. (A) Continuous wave Doppler image showing the velocity curve of the tricuspid regurgitation jet. The maximal velocity in this figure is 4.0 m/s. (B) Systolic flattening of the interventricular septum. The eccentricity index is calculated by D1/D2 and in this example is >1, indicating increased right ventricular pressure. (C) Apical 4-chamber view with an enlarged right ventricle that forms the apex and a small left ventricle. (D) M-mode of the tricuspid annulus. The systolic movement towards the apex (tricuspid annular plane systolic excursion, TAPSE) is 28 mm, which indicates normal function.

myocardial performance index, and tissue Doppler-derived tricuspid lateral annular systolic velocity (S`).[29] Lastly, echocardiography can be useful for determining the underlying cause of PH, especially in the case of left sided heart disease or congenital heart disease.

Right heart catheterisation

RHC remains the gold standard for the diagnosis of PH and is, according to the current guidelines, mandatory in every patient where PH is suspected (table 2).[1,20] Besides diagnosis, RHC can also be used in the evaluation of the effect of PH specific treatment or as confirmation in case of clinical deterioration. RHC provides information about haemodynamics, and therefore is important in the final diagnosis, classification and assessment of the prognosis of PH. Additionally, during RHC vasoreactivity testing can be performed and shunting may be detected. PVR can be calculated by dividing the TPG by the cardiac output. The TPG is the driving pressure across the pulmonary circulation—that is, the pressure difference between the mPAP ([1′ systolic PAP+2′diastolic PAP]/3) and the mean venous pulmonary pressure or PCWP.[1] The PCWP and cardiac output should always be measured in order to exclude PH due to left sided heart disease, and to calculate the TPG and PVR.[1,20] In patients without a pressure gradient over the mitral valve the PCWP equals the LV end-diastolic pressure.

Table 2. Normal values for right heart catheterisation

Pressures (mm Hg)	Systolic	Diastolic	Mean
RA			0–6
RV	15–30	0–6	
PA	15–30	7–14	9–19
PCWP			4–10
LA			4–10
LV	80–140	3–12	
Arterial O_2 saturation: 95–98%			
Mixed venous O_2 saturation: 70–75%			
Cardiac output: 4.5–7 L/min			
Cardiac index: 2.5–4.0 L/min/m^2			
PVR <120 dynes*s*cm^{-5} = <1.5 WU			
SVR <1600 dynes*s*cm^{-5} = <20 WU			

Modified with permission from Vliegen *et al.* [39]
LA, left atrium; LV, left ventricle; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; SVR, systemic vascular resistance.

In patients with PAH the increased PVR can be caused by changes in the pulmonary vasculature, but also partially by an increased vascular tone. Vasoreactivity testing is performed to determine the contribution of the increased vascular tone. The results of the vasoreactivity testing will have major implications for the treatment of PAH. Patients with a positive test may benefit from treatment with calcium channel blockers (CCBs), as demonstrated by improved survival in several studies.[31] Vasoreactivity testing is routinely performed only in patients with idiopathic PAH, hereditable PAH, and PAH associated with drugs or toxins. For patients with other forms of PAH, vasoreactivity testing should be considered on an individual basis.[1,20,31] Vasoreactivity testing may also be helpful in determining other therapeutic options for patients with PAH due to an intracardial shunt. Furthermore, a vasoreactivity test may be decisive in patients with PAH and PH due to left sided heart disease who are candidates for heart/lung transplantation. Vasodilators that can be used for vasoreactivity testing are nitric oxide (NO), epoprostenol, iloprost, adenosine, and sildenafil. According to the most recent consensus a positive test is defined as a decrease in the pulmonary artery pressure >10 mm Hg, an pulmonary artery pressure of ≤40 mm Hg, and an unchanged or increased cardiac output during the test. According to this definition, about 10–15% of idiopathic PAH patients have a positive test. A positive test does not guarantee benefit from treatment with CCBs, but is a requirement for starting treatment with these agents.[1,20,31]

TREATMENT

Lifestyle

Patients with PH require general lifestyle advice (table 3). Depending on the severity of the disease, patients should be instructed to reduce salt and fluid intake. Furthermore, physical activity should be encouraged within symptom limits. Patients should avoid excessive activity that leads to severe dyspnoea, syncope or chest pain. Participation in a supervised rehabilitation centre may be considered.[1] Other lifestyle measures that should be discussed with the patient include prevention

Table 3. Treatment of pulmonary hypertension: general measures

Lifestyle	Reduce salt and fluid intake
	Avoid pregnancy
	Infection prevention
	Avoid excessive activity
	Encourage supervised rehabilitation
	Consider psychosocial support
Supportive therapy	Oral anticoagulation therapy in IPAH, heritable PAH, drug-induced PAH and CTEPH
	Consider in associated PAH
	Diuretics in case of right sided decompensation
	Digoxin to improve cardiac output/slow ventricular rate
	Oxygen
	Antiarrhythmic drugs in case of supraventricular tachycardias

CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension.

of infection by immunization against influenza and pneumococcal pneumonia, and birth control. Pregnancy in patients with PAH has been associated with high mortality rates of 30–50% and is therefore contraindicated. Endothelin receptor antagonists (ERAs) may affect the efficacy of oral contraceptives. Moreover, administration of oxygen should be considered during travel by plane, especially in patients in New York Heart Association (NYHA) functional class III–IV or with arterial blood O_2 pressure <8 kPa. Surgery may pose an increased risk for patients with PH and should be carefully considered. If possible, epidural anaesthesia should be used, because this is generally better tolerated by PH patients than general anaesthesia. Finally, psychosocial support should be considered because of the poor quality of life of these patients.[1]

Supportive therapy

In PAH there is evidence of coagulopathies with increased risk of thrombosis.[32] Therefore the use of oral anticoagulation, in the absence of contraindications, should be considered in PAH. CTEPH patients should receive lifelong anticoagulation therapy. Diuretics are recommended in the case of right sided decompensation; the volume overload of the RV causes functional TR. The use of diuretics can reduce the severity of the TR, improving the output of the RV. Digoxin may be helpful for inotropic support in a number of patients. The maintenance of sinus rhythm is important in the treatment of PH, as persistent atrial fibrillation is associated with an increased mortality and onset of supraventricular tachycardia can result in clinical deterioration and/or RV failure.[33] Therefore, treatment with antiarrhythmic drugs should also be considered. The use of long term oxygen therapy should be encouraged in patients with hypoxia, because the hypoxic mediated vasoconstriction may be reduced.[1]

PH specific therapy

Currently available drug therapies that target the pathologic pathways in PH do not cure the disease but are meant to reduce the PVR, pulmonary pressures and symptoms. These days, several classes of PH specific drugs are available (figure 5).

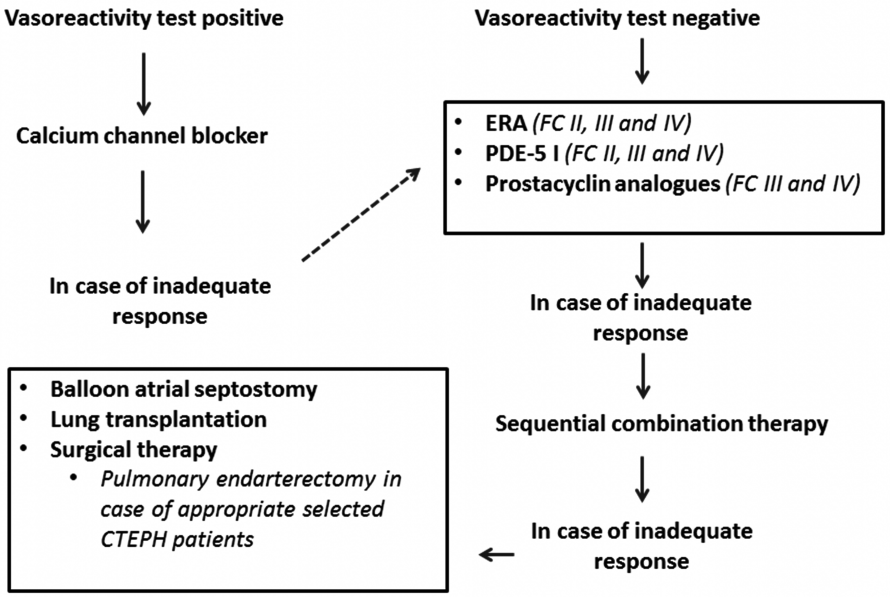

Figure 5. Treatment of pulmonary hypertension: PAH specific measures. CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonists; FC, functional class; PAH, pulmonary arterial hypertension; PDE-5 I, phosphodiesterase type-5 inhibitor.

Prostacyclin analogues are potent pulmonary vasodilators. In PAH patients, there is a down-regulation of prostacyclin synthase causing a relative deficiency of prostacyclin. Prostacyclin induces a potent vasodilation of all vascular beds. Epoprostenol was the first available short-acting pulmonary vasodilator. It was shown to improve exercise capacity, quality of life and survival in patients with idiopathic PAH and other forms of PAH.[34] However, epoprostenol has to be administered by continuous intravenous infusion and has serious dose dependent adverse effects. Other prostacyclin analogues are treprostinil, which has a longer half-life compared to epoprostenol, and iloprost, which can be inhaled. Prostacyclin analogues are recommended in patients with PAH in NYHA functional class III and IV.[1,20]

The use of ERAs followed the successful introduction of the prostacyclin analogues. An important advantage of ERAs is that they can be administered orally. Activation of endothelin-1 has been demonstrated in PAH, which causes vasoconstriction in the pulmonary vasculature by binding two endothelin receptors, subtypes A and B. ERAs either bind both receptors or one selective receptor. Bosentan is a dual ERA that has been demonstrated to improve functional class, haemodynamics, and time to clinical worsening.[1,35] A major disadvantage of bosentan is the risk of an increase in hepatic aminotransferases in ~10% of patients, requiring monthly control of liver enzymes. This risk can occur any time during the use of bosentan. Ambrisentan is an ERA that is selective for the endothelin receptor subtype A and reduces the risk of elevation in hepatic enzymes. However, monthly testing of liver enzymes is required in patients taking ambrisentan. The new ERA macitentan probably has no effect on liver enzymes. In addition, it has been shown to reduce morbidity and mortality in PAH. ERAs are recommended in PAH patients in NYHA functional class II and III.[1]

Another group of PH specific drugs are the phosphodiesterase-5 inhibitors (sildenafil and tadalafil), which inhibit the cGMP-degrading enzyme phosphodiesterase type 5 and cause vasodilatation through the NO/cGMP pathway. Sildenafil demonstrated similar results in improving exercise tolerance, symptoms and haemodynamics, as was previously demonstrated by the use of ERAs.[36] Phosphodiesterase-5 inhibitors are recommended in patients in NYHA class II and III.

The majority of PAH patients will eventually receive combination therapy, which is the simultaneous use of two or more PH specific drugs. Combination therapy is recommended in patients who do not show an adequate response to treatment with a single PH specific drug. There are, however, uncertainties regarding the optimal timing and sequential combination.[1]

Although patients in groups 2–4 of the PH classification are much more common than PAH patients, fewer data are available on medical therapy in these groups of patients than in the PAH group. So far, there have been no large randomized clinical trials performed in non-PAH groups addressing the effects of PAH specific treatment. Therefore, the underlying disease should be treated.[12]

Surgical treatment

In appropriate selected CTEPH patients pulmonary endarterectomy can be curative. However, not all CTEPH patients are candidates for this surgical therapy, and in a subgroup (10–15%) of CTEPH patients receiving pulmonary endarterectomy PH persists or recurs.[37] In these patients PH specific treatment can be beneficial, and there are several studies indicating improvement in haemodynamics and clinical condition.[12]

PH patients in NYHA functional class IV with right heart failure who do not respond to PH specific drug therapy should be considered for balloon atrial septostomy or heart/lung transplantation. By creating an intra-atrial right–left shunt, the RV will be decompressed and the cardiac output will be increased. This intervention should only be considered in patients with arterial oxygen saturation > 80%.[1,38] Patients with indicators of poor prognosis despite maximal medical therapy should be referred for transplantation.[1]

CONCLUSION

PH is a complex condition that challenges the clinician, both in the diagnosis and in the treatment of the disease. Nowadays, it is customary to evaluate and treat PH patients in a dedicated PH centre by a multidisciplinary team. It is essential to diagnose the underlying cause, because this has profound consequences for the therapeutic strategies. Furthermore, it is important to recognize PH and start treatment at an early stage of the disease, as this will improve prognosis.

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