Pulmonary Arterial Hypertension in Intensive Care Unit

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Key Points

- In critically ill patients, the diagnosis of pulmonary arterial hypertension (PAH) is difficult as it can easily be confounded with other forms of pulmonary hypertension (PH).
- PAH is a form of PH. On the opposite, PH does not automatically imply PAH.
- The main cause of PH in ICU is left cardiac failure, followed by chronic pulmonary disease and chronic thromboembolic disease.
- Idiopathic is the most frequent cause of PAH, but PAH can also be associated with scleroderma, HIV infection, anorexigen toxicity, thyroid disease, cirrhosis.
- Pulmonary vasodilators allow a significant improvement of the prognosis in outpatient. In ICU, pulmonary vasodilators should be only a part of a general management including: treatment of triggering factors, optimization of fluid balance, decrease of RV afterload by using pulmonary vasodilators while maintaining cardiac output and mean arterial pressure.
- The early contact of PH referral center or specialized physician is of particular importance.

Introduction

Pulmonary arterial hypertension (PAH) is a rare, severe and complex disease. When the diagnosis is suspected, a multidisciplinary approach involving at least a PAH-

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specialized physician is recommended as highly specific treatment (in particular pulmonary vasodilators) can be indicated. In the absence of specific treatment, death occurs in the 3 years following diagnosis [1]. For the intensive care unit (ICU) physician, the diagnosis of pulmonary arterial hypertension (PAH) is difficult as it can easily be confounded with other forms of pulmonary hypertension (PH). The key issue is that PAH is a form of PH. On the opposite, PH does not automatically imply PAH. Pulmonary arterial hypertension must be differentiated from other causes of PH that are frequently seen in ICU. It was recently emphasized that pulmonary veno-occlusive disease (PVOD) must be differentiated from PH and PAH.

In critically ill patients, acute PH is frequently observed, especially in case of severe hypoxia due to acute respiratory distress syndrome or severe pulmonary embolism (PE) [2, 3]. In this case, acute PH is due to reflex and reversible hypoxic pulmonary vasoconstriction. The second cause of acute PH in ICU patient is acute left ventricle failure that increases left atrial pressure and, as a consequence, pulmonary artery pressure ("post capillary" PH). Acute PH is a reversible phenomenon when hypoxia and/or left atrial pressure are rapidly controlled. This should be differentiated from chronic PH that can be due to various chronic diseases. In ICU patients, chronic PH is also frequently seen in the evolution of chronic obstructive pulmonary disease (COPD), thromboembolic disease or chronic left heart failure. Beyond these three mains causes of chronic PH, the intensivist have to keep in mind that PH can be associated to rare chronic diseases that should not be under diagnosed because they imply a specific treatment. The more frequent of these rare diseases is PAH. The accurate diagnosis of PAH is of crucial importance since it implies a specific treatment by selective pulmonary vasodilators.

The diagnosis of PAH in ICU is a triple challenge. *First*, acute pulmonary hypertension must be distinguished from chronic pulmonary hypertension. *Second*, when chronic PH is diagnosed, a systematic screening of all potential causes of PH must be performed in order to exclude or diagnose PAH because PAH implies a specific treatment with pulmonary vasodilators. *Third*, when PAH is suspected, the last challenge is to test the clinical response to pulmonary vasodilators and to choose the best pharmacological class. In case of respiratory symptoms worsening after administration of pulmonary vasodilators, a PVOD should be suspected.

In the present text, we will only discuss clinical and therapeutic features of PAH and PVOD in ICU patients that correspond to the Class 1 and 1′ of the actual PH classification [4].

Definition and Classification

Pulmonary hypertension is the main sign of PAH. Pulmonary hypertension is a wide syndrome defined as a non-specific elevation of the pulmonary artery pressure at rest, whatever the etiology [5]. Pulmonary hypertension is defined as

a mean PAP (mPAP) >25 mm Hg as assessed by right heart catheterization (RHC). Echocardiography is very useful to screen patients with suspected PH but it cannot replace RHC. The criterion based on systolic pulmonary pressure (sPAP) >35 mm Hg should be abandoned. The criterion based on exercise PAP values (mPAP >30 mm Hg on exercise) should no longer be used, as they are not supported by strong published data. Moreover, on exercise, healthy individuals can reach much higher of mPAP values [5].

The first classification of PH published in 1973 by the World Health Organization (WHO) [6] stated that PH should be divided in two categories: secondary or primary PH. This pragmatic approach is apparently well adapted to critically ill patients but it nowadays appears as too simple. As evoked in introduction section, in ICU patients, "secondary" chronic PH is frequently observed as a final consequence of chronic diseases as left ventricle failure (post capillary chronic PH), chronic thromboembolic pulmonary disease or severe chronic obstructive pulmonary disease (COPD). In 1973, primary PH referred to PH with no obvious cardiovascular or pulmonary cause. It was further demonstrated that "primary" PH was a complex and non-homogeneous group of diseases that could be primary (idiopathic), but also associated with various diseases ranging from connective tissue disease or cirrhosis to drug toxicity or human immunodeficiency virus (HIV) infection. Therefore, the risk of the original classification was to under-diagnose rare causes of PH that needs a specific treatment. Then, a more complex classification was proposed in 1998 (*Evian* classification [7]) and updated in 2003 (*Venice* classification [8]) and 2008 (*Dana point* classification, published in 2009 [5]). The actual classification (*Dana point*) is shown in Table 1. The three main evolutions of the new classification were (1) to stop the use of primary/secondary HP classification, (2) to separate PH from pulmonary arterial hypertension (PAH), (3) to separate PAH from veno-occlusive pulmonary disease and/or hemagiomatosis [4, 5, 9]. The evolution of clinical classification of PH during the 3 past decades is summarized in Table 1. Pulmonary arterial hypertension (PAH = Class 1) refers to a heterogeneous group of non-cardiac, non-pulmonary diseases characterized by a chronic PH. The main causes of PAH are: idiopathic, heritable, drug-induced, associated (HIV infection, connective tissue disease, portal hypertension, congenital heart disease, schistosomiasis, chronic hemolytic anemia) and persistent PH of the newborn. In this classification, pulmonary hypertension refers to a PH due to an obvious pulmonary or cardiac cause. The three mains causes of PH are cardiac (severe congestive left heart failure, Class 2), pulmonary (COPD, Class 3) and thromboembolic (Class 4) (Table 1). A fourth cause of PH is proliferative diseases as hematologic diseases, storage diseases or anatomical obstruction of pulmonary vessels by fibrosis or tumor (Class 5). These four PH classes represent the "secondary" PH of the original classification. Finally, an intermediate class (Class 1′) is a direct pulmonary vessels disease called pulmonary veno-occlusive disease (PVOD) and/or capillary hemangiomatosis. The diagnosis of PVOD may be difficult because since it can mimics left ventricle failure.

Table 1 Updated clinical classification of pulmonary hypertension (Dana Point 2008) [5]

1 Pulmonary arterial hypertension (PAH)
This class refers to "primary" PH of the initial classification (1973)
1.1 Idiopathic (IPAH)
1.2 Heritable *(formerely familial—2003)*
1.2.1 BMPR2
1.2.2 ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3 Unknown
1.3 Drugs and toxins induced: fenfluramine derivatives, aminorex, rapeseed oil
1.4 Associated with (APAH)
1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease: Eisenmenger's syndrome[a], Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts[b], adult pulmonary arterial hypertension with small defect[c], Pulmonary arterial hypertension after corrective cardiacsurgery[d]
1.4.5 Schistosomiasis
1.4.6 Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis.
This class refers to "primary" PH of the initial classification (1973)
This class was separated from class 1 as compared to the 2003 classification
2 Pulmonary hypertension (PH) due to left heart disease
This class refers to "secondary" PH of the initial classification (1973)
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3 PH due to lung diseases and/or hypoxia
This class refers to "secondary" PH of the initial classification (1973)
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 (PH)
This class refers to "secondary" PH of the initial classification (1973)
5 PH with unclear and/or multifactorial mechanisms
This class refers to "secondary" PH of the initial classification (1973)
5.1 Haematological disorders: myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis

(continued)

Table 1 (continued)

5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 activin receptor-like kinase 1, *APAH* associated pulmonary arterial hypertension, *BMPR2* bone morphogenetic protein receptor, type 2, *HIV* human immunodeficiency virus, *PH* pulmonary hypertension

Italics: comparison with previous classifications (1973 and 2003)

[a] Eisenmenger's syndrome includes all systemic-to-pulmonary shunts due to large defects leading to a severe increase in PVR and resulting in a reversed (pulmonary-to-systemic) or bidirectional shunt. Cyanosis, erythrocytosis, and multiple organ involvement are present

[b] Pulmonary arterial hypertension associated with systemic-to-pulmonary shunts. In these patients with moderate to large defects, the increase in PVR is mild to moderate, systemic-to-pulmonary shunt is still largely present, and no cyanosis is present at rest

[c] Adult pulmonary arterial hypertension with small defects : in cases with small defects (usually ventricular septal defects, 1 cm and atrial septal defects, 2 cm of effective diameter assessed by echocardiography) the clinical picture is very similar to idiopathic PAH

[d] Pulmonary arterial hypertension after corrective cardiac surgery. In these cases, congenital heart disease has been corrected but PAH is either still present immediately after surgery or has recurred several months or years after surgery in the absence of significant post-operative residual congenital lesions or defects that originate as a sequela to previous surgery

Epidemiology

Pulmonary artery hypertension is characterized by a progressive increase of pulmonary artery resistances and chronic right ventricle failure. Chronic right heart failure is the main prognostic factor of PAH. The prevalence is probably underestimated because of the poor specificity of clinical signs. In a population of patients evaluated by echocardiography for dyspnea, the prevalence of PH was about 10 %. On the population of patients with PH echocardiographic signs, about 80 % had left heart failure, 10 % had chronic pulmonary disease and hypoxia, 4 % had PAH, 0.6 % had thromboembolic disease [10]. The prevalence of PAH ranges from 15 to 50/million adult population [11]. Idiopathic PAH (IPAH) is the most common cause of PAH. In a population of patient with documented PAH, 39.2 % of patients has IPAH and 3.9 % had family history of PAH. In the subgroup of associated PAH, 15.3 % had connective tissue disease, 11.3 % had congenital heart disease, 10.4 % had portal hypertension, 9.5 % had anorexigen-associated PAH and 6.2 % had HIV infection [12]. Pulmonary artery hypertension is a severe and insidious disease. The non-specific signs of PAH are associated with a delayed diagnosis that worsens prognosis. Before 2000, there were few specific treatment and few specialized teams for PAH care. At that time, the mean survival time was low (2.8 years following diagnosis) with survival rates of 68, 48, and 34 % at 1, 3, and 5 years, respectively [1]. Since the introduction of specific vasodilators (in particular epoprostenol) and specialized teams, the prognosis significantly improved as the reported survival at 1, 3, and 5 years was 87.8, 76.3, and 62.8 % in USA registry and 87, 76 and 67 % in the French registry, respectively [1, 13]. If these results are encouraging, the prognosis remains severe, especially when ICU

admission is required. In ICU, the prognostic of PH or PAH is considered as poor but few data are available. Therefore, no strong recommendation for PH or PAH treatment in ICU patients can be done [14, 15]. In a population of 82 septic ICU patients with history of PH mainly due to pulmonary disease, the mortality was related to the severity of PH. In mild, moderate or severe PH, the mortality was 28, 67 and 80 %, respectively [16]. Therefore, in patients with end-stage PH in whom all available treatment options have been exhausted, limitations on advanced treatment and/or ICU admission should be discussed [15].

Physiopathology Insights

Pulmonary arterial hypertension is characterized by the progressive increase in pulmonary arterioles (500 microns diameter) resistance. This induces right ventricle failure that is strongly associated to death. Right ventricle tolerance to PH is highly variables among subjects. As numerous chronic severe diseases, PAH mechanisms are multiple, complex and not well identified [5]. Genetic factors have been identified in PAH. Heritable PAH represents less than 10 % of cases. Heritable PAH is an autosomal dominant disease with incomplete penetrance. Mutations of *transforming growth factor beta* (TGF-β) receptors genes were identified as responsible of heritable but also sporadic cases. In particular, mutations of *bone morphogenetic protein recepetor*-2 (BMPR2) or *activin-like receptor* 1 (ALK-1) were shown to be associated with PAH and hereditary hemorrhagic telangiectasia, respectively (Class 1, 2, Table 1). The three mains pathophysiologic findings reported in autopsy studies are (1) abnormal vascular cell proliferation (low apoptosis/proliferation ratio) inducing arteriolar remodeling, (2) excessive vasoconstriction and (3) partial thrombotic phenomenon. Pregnancy should be discouraged since it can worsen PAH.

Diagnosis

Clinical Diagnosis of PAH [4, 5, 8, 12]

The first step of diagnosis approach is to eliminate clinical signs of COPD (or other chronic pulmonary parenchymal disease), of congestive left heart failure and of thromboembolic disease. If such signs are present, the diagnosis of PAH is unlikely and Class 2, 3 and 4 PH should be suspected and explored. The presence of signs of hematologic, malignant, vasculitis or storage disease is unlikely in PAH. In this case, a class-5 PH (Table 2) must be suspected and explored.

If no signs of class 2, 3, 4 and 5 PH are present, PAH can be suspected. The onset of disease is insidious, with low specific functional signs. The most common symptom is breathlessness, particularly on exercise (60 %), followed by fatigue

(19 %), syncope (8 %), angina (7 %), lipothymia (5 %), leg edema (3 %) [17]. Data obtained from the French national registry published in 2006 shows the following characteristics [12]. The female/male sex ratio is 1.9. The mean age is 50 ± 15 years. Body mass index (BMI) is usually normal. A BMI above 30 is observed in 15 % of the cases, similar to the adult French population. The delay between onset of symptoms and diagnosis is 27 months. A majority (75 %) of patients had severe symptoms at presentation, with a New York Heart Association (NYHA) functional class III or IV (class I = 1 %, class II: 24 %). Exercise capacity is tested through a 6-minute walk test, which was abnormal (329 ± 109 m) in most patients. The six-minute walk distance is correlated with NYHA functional class.

In PAH Symptoms at rest are seen only in advanced cases. The physical examination shows left parasternal lift, accentuated pulmonary component of second heart sound, systolic murmur of tricuspid regurgitation, diastolic murmur of pulmonary insufficiency and right ventricle third sound. In the more advanced states, functional symptoms are present at rest and physical examination shows jugular vein distension, hepatomegaly, peripheral edema, ascites, and cool extremities. Lung sounds are usually normal in PAH. The presence of basal crackles may point towards interstitial lung disease or left cardiac failure. Nevertheless, physicians have to keep in mind that basal crackles can be seen in PVOD. A cyanosis can be seen in 20 % of IPAH cases and suggests right-to-left shunting and severe reduction of cardiac output. Digital clubbing is not frequent in IPAH but when present, a congenital heart disease or a PVOD should be suspected. Telangiectasia, digital ulceration, and sclerodactily are seen in scleroderma. Finally, clinical examination tries to identify or exclude stigmata of chronic liver disease.

The diagnosis of POVD should be suspected in case of symptoms worsening after administration of selective pulmonary vasodilator. The presence of pulmonary edema signs associated with RV failure without evidence of LV failure is also highly suggestive of POVD. In the evolution of PAH, low cardiac output can be associated with bacteremia due to gut bacteria translocation that can lead to death.

Electrocardiography

Electrocardiography is classically normal at the early stage of IPAH. Electrocardiograpm has low sensibility (55 %) and specificity (70 %) and cannot be used alone as a screening tool for the diagnosis of PH or PAH. The association of right axis deviation, pulmonary P wave, R/S wave ratio >1 in V1 lead and R wave >0.5 mV has a 90 % specificity for RV failure. This is of poor prognosis during PAH. Ventricular arrhythmias are rare. Supraventricular arrhythmias may be present in advanced stages (in particular atrial flutter and atrial fibrillation) and always leads to further clinical deterioration.

Table 2 World Health Organization (WHO) functional classification of pulmonary hypertension modified after the New York Heart Association (NYHA) functional classification

Class I
Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
Class II
Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class III
Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class IV
Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

Biology

There is no specific biomarker of PAH. The brain natriuretic peptide (BNP) is elevated due to right atrial and/or ventricle dilation. The BNP value is correlated to prognosis. Liver tests may be abnormal either in case of RV failure or in case of PAH associated with cirrhosis. Differentiating one from the other cause may be difficult. In this case, clinical evaluation and morphologic hepatic evaluation are of paramount importance. Serologic tests for HIV infection and hepatitis are mandatory. Thyroid tests are also useful (Class5 PH). When a connective tissue disease (CTD) is suspected, auto immunity tests should be performed. Antinuclear antibodies are not specific of CTD-APAH. About 40 % of patients with IPAH have elevated anti-nuclear antibodies, usually in low titre (1:80). Scleroderma is the CTD with the highest prevalence of PAH. Anti-centromere antibodies are typically positive in limited scleroderma as are other anti-nuclear antibodies including dsDNA, anti-Ro, U3-RNP, B23, Th/To, and U1-RNP. In the diffuse variety of scleroderma, U3-RNP is typically positive. In case of systemic lupus erythematosus, anti-cardiolipin antibodies may be found. Thrombophilia screening (antiphospholipid antibodies, lupus anticoagulant, and anti-cardiolipin antibodies) should be performed when chronic thromboembolic PH is suspected [5].

Chest X Ray

The main interest is to eliminate obvious sign of PH associated with chronic pulmonary (COPD, emphysema or interstitial disease) or left cardiac failure (infiltrates associated with congestive heart failure). However, Chest X ray is

usually abnormal at the time of PAH diagnosis. The typical findings are central pulmonary artery dilation which contras with peripheral vascular loss. The enlargement of right atria and ventricle are seen in advanced cases.

Echocardiography

Echocardiography is the best tool for PAH screening when suspected. Transthoracic echocardiography (TTE) is usually sufficient to diagnose PH and assess RV function that remains the main prognostic factor in PAH. Echocardiography does not exclude the need for RHC, which remains mandatory in all suspected cases of PAH. Echocardiography is nowadays widely available in ICU [18] and plays a fundamental role in cardiac and hemodynamic assessment in critically ill patients [19, 20], especially in case of RV failure or PH [21]. Figure 1 shows an example of severe IPAH in a patient admitted to ICU for a septic shock due to invasive diarrhea.

First Step: Echocardiography Diagnosis of PH, Estimation of Systolic PAP Value

Because patients with PAH admitted in ICU are usually at advanced stage of the disease, echocardiography findings are usually easy to diagnose. The first difficulty is to separate acute from chronic PH. In case of acute PH, sPAP value is rarely more than 40 mm Hg. Above such value, RV cannot compensate acute afterload increase and right cardiac output (CO) decreases. The subsequent low CO limits the sPAP increase, which rarely reaches more than 40–45 mm Hg. The consequence of acute RV failure is a rapid (few hours) dilation of RV. As pericardium is not distensible in a short period of time, the biventricular volume is constant. Therefore, the hemodynamic consequence of acute RV dilation is LV compression, which limits LV filling and subsequently worsens low cardiac output. For those reasons, when a sPAP value is more than 40 mm Hg, a chronic PH is likely. In chronic PH, the simplest way to assess sPAP is to record tricuspid regurgitation (TR) flow on a four-chamber apical view (Table 3). The maximal velocity of TR is correlated to the pressure gradient between pulmonary artery and RV (Table 3). This approach can also be applied to pulmonary regurgitation that require a trained operator. Pulmonary regurgitation flow allows evaluation of mean and diastolic pulmonary artery pressure (Table 3). The sum of right atrial pressure or central venous pressure (RAP, CVP) value and right ventriculo-arterial gradient represent sPAP (Table 3). Evaluation of RAP value by TTE is summarized in Table 4. A semiquantitative approach of sPAP can be done on the basis of gradient only (Table 3). The acceleration time of pulmonary ejection flow allows a semi-quantitative assessment of sPAP for trained operators when TR is not recordable. (Table 3)

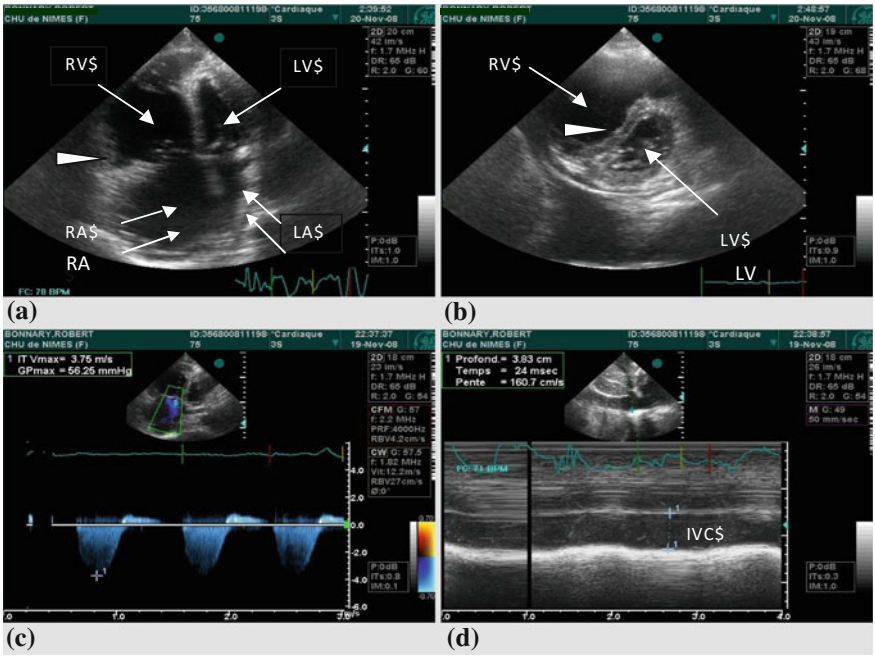

Fig. 1 Echocardiography diagnosis of pulmonary hypertension. Idiopathic pulmonary arterial hypertension with chronic right ventricle failure in a 68 years-old patient admitted in ICU for septic shock in intensive care unit. **a** Four chambers apical view showing a major right atrial and ventricle (RV) dilation. The RV free wall is thickened (white triangle) due to a chronic adaptation to chronic pulmonary hypertension. **b** Parasternal short axis view. Paradoxical septum (white triangle) with typical left ventricle of "D sign". In physiological condition, LV shape is circular ("O sign"). **c** Tricuspid regurgitation recoeder by continuous Doppler. Maximal velocity (Vmax) = 3.75 which correspond to a RV/PA gradient equal to 56 mm Hg ($\Delta P = 4\ V^2$). **d** Recording of inferior vena cava (IVC) by M mode in a subcostal view. The IVC diameter is 38 mm and no respiratory variation is observed. The RAP value is over than 20 mm Hg (See Table 3). In this case, systolic pulmonary artery pressure is 56 + 20 = 76 mm Hg. This was consistent with the value measured by pulmonary artery catheter (80 mm Hg)

Second Step: Eliminating Left Systolic and/or Diastolic Failure, Advanced Valvular Disease and Screening for Eisenmeger's Syndrome

As mentioned in epidemiology section, left heart failure is the main cause of PH. One of the main roles of TTE is to exclude systolic or diastolic LV dysfunction. The quantification of systolic function is usually simple, visually or by LV ejection fraction measurement. Assessing diastolic function can be more difficult. Clinical and echocardiography criteria for suspecting PH secondary to LV failure (especially diastolic) are summarized in Table 5. The intensivist can perform them. It includes LV ejection fraction, Mitral inflow Doppler pattern, tissue Doppler pattern at the lateral and medial mitral annulus, pulmonary venous flow. The intensivist can also perform the diagnosis of advanced valvular disease. However, diagnosis of

Table 3 Echocardiography assessment of pulmonary artery pressure by echocardiography

Evaluation of sPAP by tricuspid regurgitation velocity in apical four chamber view (simple technique)
Pressure gradient between RV and PA: $\Delta P = 4. (RT\ Vmax)^2$
$sPAP = \Delta P + RAP$
Semiquantitative assessement of sPAP by tricuspid regurgitation velocity in apical four-chamber view assuming a RAP value of 5 mm Hg (the simplest technique)
Echocardiographic diagnosis: PH unlikely
Tricuspid regurgitation velocity = 2.8 m/s, PA systolic pressure = 36 mm Hg
No additional echocardiographic variables suggestive of PH
Echocardiographic diagnosis: PH possible
Tricuspid regurgitation velocity = 2.8 m/s, PA systolic pressure = 36 mm Hg
Presence of additional echocardiographic variables suggestive of PH
Tricuspid regurgitation velocity = 2.9–3.4 m/s, PA systolic pressure = 37–50 mm Hg
With/without additional echocardiographic variables suggestive of PH
Echocardiographic diagnosis: PH likely
Tricuspid regurgitation velocity = 3.4 m/s, PA systolic pressure = 50 mm Hg
With/without additional echocardiographic variables suggestive of PH
Exercise Doppler echocardiography is not recommended for screening of PH
Evaluation of sPAP by pulmonary ejection flow acceleration time in short axis view (for trained operators, when TR is not recordable)
Tacc <100 ms = PH, Tacc <60 ms = severe PH
Evaluation of sPAP by pulmonary regurgitation flow (for trained operators, when TR is not recordable)
Pulmonary regurgitation flow have a maximum velocity that evaluates mPAP (mPAP = 4.Vmax2 + RAP) and a minimum velocity which correspond to dPAP. The sPAP is obtained by the following formula: sPAP = 3 mPAP–2 dPAP

Vmax maximal velocity, *PAP* pulmonary artery pressure, sPAP *systolic PAP*, *mPAP* mean PAP, *dPAP* diastolic PAP, *RAP* right atrial pressure, *Tacc* pulmonary ejection acceleration time, *PH* pulmonary hypertension, *ΔP* pressure gradient between right ventricle and pulmonary artery

Table 4 Echocardiographic assessment of right atrial pressure (RAP) by analysis of inferior vena cava (IVC) diameter and its respiratory variations (collapsibility of IVC: cIVC)

IVC diameter	cIVC (%)	RAP (mm Hg)
Low: <15 mm	>50	0–5
Normal: 15–25 mm	>50	6–10
	<50	11–15
High: >25 mm	<50	16–20
	None	>20

Eisenmenger's syndrome is difficult and must be done by a cardiologist specialized in such diseases.

Third Step: Assessment of Right Ventricle Function

The main sign of RV failure is dilation. The RV dilation can be visually assessed [22] or by calculation of RV/LV end diastolic area (Fig. 2). In chronic RV failure,

Table 5 Clinical and echocardiography criteria for the diagnosis of PH related to of left ventricular systolic or diastolic dysfunction. Adapted from [5]

Clinical features
Age >65
Elevated systolic blood pressure
Elevated pulse pressure
Obesity, metabolic syndrome
Hypertension
Coronary artery disease
Diabetes mellitus
Atrial fibrillation
Echocardiography
LVEF <40 %, visually or by Simpson approach. The S wave velocity at the lateral mitral annulus can also be used (Normal >8 cm/s, equivalent to LVEF >50 %) in the absence of regional severe wall motion anomaly.
Left atrial enlargement
Concentric remodelling of the LV
LV hypertrophy
Presence of echocardiographic indicators of elevated LV filling pressure: E/A ratio >2, E wave velocity >90 cm/s, E/E′ ratio >15, S/D ratio of pulmonary venous flow <1.
Evaluation over time
Symptomatic response to diuretics
Exaggerated increase in systolic blood pressure with exercise
Concomitant decrease of sPAP and LV filling pressure after diuretics
Re-evaluation of chest radiograph consistent with heart failure

LVEF left ventricle ejection fraction, *LV* left ventricle, *sPAP* systolic pulmonary artery pressure

the RV free wall is thickened (normal value <6 mm). The RV systolic function can be evaluated by the tricuspid annulus plane systolic excursion (TAPSE) in M-mode. The normal value of TAPSE is 16–25 mm. A TAPSE value inferior to 15 mm is of poor prognosis [5]. This index represents the maximal anterior systolic displacement of tricuspid annulus. This simple and reproducible index is correlated with RV ejection fraction (RVEF). An analogous method could be applied to tissue Doppler at the lateral tricuspid annulus. The maximal velocity of S (systolic) wave recorded by tissue Doppler at the lateral tricuspid annulus is correlated to RVEF. A S velocity value inferior to 11 cm/s correlates with altered RVEF whereas a value inferior to 9 cm/s is correlated with sever alteration of RV systolic function. The existence of pericardial effusion is associated with bad prognosis [5].

Thoracic CT Scan

Performing CT scan is of mandatory for the diagnosis of PAH, especially in order to exclude pulmonary, cardiac or thromboembolic cause of PH. Contrast CT angiography of the pulmonary artery show the typical angiographic findings in

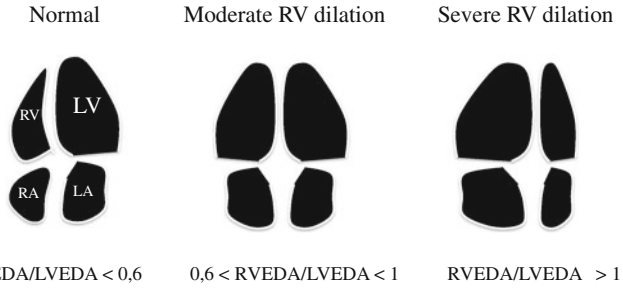

Fig. 2 Echocardiography visual assessment of right ventricle dilation. The main sign of right ventricle failure is dilation. *RVEDA* right ventricle end diastolic area, *LVEDA* left ventricle end diastolic area

chronic thromboembolic PH (Class 4) such as complete obstruction, bands and webs, and intimal irregularities as accurately and reliably as conventional angiography. High-resolution CT scan gives important informations on lung parenchyma. It can easily identify interstitial lung disease, advanced COPD and emphysema. It can also be helpful in case of clinical suspicion of PVOD. The presence of interstitial edema with diffuse central ground-glass opacification and thickening of interlobular septa suggest PVOD. In this disease, CT scan may also show lymphadenopathy and pleural effusion. A diffuse bilateral thickening of interlobular septa associated with small centrilobular poorly circumscribed nodular opacities can help to diagnose pulmonary capillary hemangiomatosis.

Right Heart Catheterization

Outside the ICU

A right heart catheterization is obligatory to confirm the diagnosis of PAH. It allows to exclude other causes of PH, in particular post capillary PH. It is the sole way to test the vasoreactivity of pulmonary vessels to selective pulmonary vasodilators in order to evaluate the usefulness of subsequent chronic treatment. In outpatients, the complication rate of RHC is low in experienced centers [23]. In a study evaluating 7218 RHC procedures, the complication rate was 1.1 % (IC 0.8–1.3), related to difficult vascular access, arrhythmias or hypotension. Four death were reported but only one was directly attributable to RHC. RHC must record staged measurement of SaO2, RAP, RV pressure, PAP (systolic, diastolic and mean), PA wedge pressure (that reflects left atrial pressure), cardiac output, cardiac index and pulmonary vascular resistances. The RHC criteria for PAH are summarized in Table 6. At the time of diagnosis, mPAP value is 50 ± 17 mm Hg NYHA class I–II patients and 56 ± 15 mm Hg NYHA III–IV class patients [12].

Table 6 Right heart catheterization criteria for PAH diagnosis

mPAP at rest >25 mm Hg
Pulmonary artery wedge pressure (PAwP) <15 mm Hg
Pulmonary vascular resistances ([mPAP-PAwP]/CO) >3 Wood units
A PawP >15 mm Hg associated with a dPAP—PawP gradient >10 mm Hg is seen in PAH from arterial and venous origin

mPAP mean pulmonary arterial pressure, *dPAP* diastolic pulmonary artery pressure

The RHC can be useful for the diagnosis of PVOD. When the catheter extremity is in wedge position, a saline flush leads to a marked pressure increase followed by a very slow pressure decrease. This phenomenon is due to a trapping of saline between the catheter and the occluded veins. If a wedge pressure can be recorded (this may be difficult), a low value is classical whereas capillary pressure is high. This can be indirectly assessed by the difference between dPAP and PAwP.

The vasoreactivity test must be performed in every cases of suspected PAH. This test aims to identify patients that can benefit from selective or non selective pulmonary vasodilators. A positive response to vasoreactivity test is more frequent in IPAH than in other categories of PAH. The test is performed during the RHC procedure. It can use IV epoprostenol IV at a dose ranging from 2 to 10 ng/Kg/min (incremental dose of 2 ng/Kg/min every 15 min), or IV adenosine at a dose ranging from 50 to 250 mcg/Kg/min (incremental dose of 50 mcg/Kg/min every 2 min), or inhaled nitric oxide (NO) at a dose ranging from 10 to 80 ppm (fixed dose, no incremental administration needed). Inhaled NO is the best pharmacological agent because of a strong selectivity for pulmonary vessels. In clinical practice, inhaled NO is administered at a dose of 24 to 40 ppm over 5 min. At that time, new RHC measurements are performed, with ongoing NO administration. A positive response is defined as a 10 mm Hg mPAP decrease associated with an absolute value below 40 mm Hg with no concomitant cardiac output decrease. For non IPAH, the probability of positive response is low. This test can be harmful in case of elevated left filling pressure.

In the Context of ICU

The RHC can be dangerous in decompensated patients. Moreover, decompensated patients may have transient elevated PA pressure. Therefore, pressure criteria must be difficult to interpret. In such case, the positivity of vasoreactivity test is more important than absolute PAP value. In ICU, right heart catheterization can be difficult in case of severe PAH [24]. Despite these restrictions, RHC is mandatory for IPAH diagnosis in ICU patients when diagnosis is suspected.

Table 7 Determinants of poor prognosis in PAH

Clinical evidence if right ventricle failure
Rapid rate of progression of symptoms
Syncope
NYHA functional class = III–IV
Six minutes walk test <300 m
Peak O_2 consumption <12 mL/min/Kg
High elevated BNP or NT-proBNP plasma levels
Echocardiography findings: TAPSE <15 mm and/or pericardial effusion
Right heart catheterization findings : RAP >15 mm Hg or CI <2 L/min/m^2

NYHA New York Heart Association, *BNP* brain natriuretic peptide, *TAPSE* tricuspid annulus plane systolic excursion, *RAP* right atrial pressure

Prognosis (Table 7)

The prognosis depends on the severity of RV failure and the etiology. The worse prognosis is seen in PAH associated with scleroderma. Whatever the cause, treatment by a selective pulmonary vasodilator (when indicated) has a favorable impact on outcome [25].

Traitement (Fig. 3)

Outside the ICU

General measures: oxygen therapy, diuretics in case of edema and/or RV failure, anticoagulants and digoxin in case of arryhtmias. Pregnancy, altitude travel, important exercise are classically contra-indicated.

Specific treatments (Table 8): calcium blockers, selective endothelin inhibitors (ERA), prostacyclin analogous, phosphodiesterase type 5 inhibitors (IPDE). Riociguat, a soluble guanylate cyclase stimulator, has been show in a phase III study (PATENT-1 trial) to significantly improved exercise capacity by week 12. This molecule improved the 6-minute walk distance both in patients who were receiving no other treatment for the disease and in those who were receiving endothelin-receptor antagonists or prostanoids. There were significant improvements in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, time to clinical worsening, and dyspnea score [26]. Encouraging results were also recently reported with riociguat in case of thromboembolic PH [27]. In the past, most studies involving the therapies listed in Table 8 were short-term trial with exercise capacity as a primary end point. Macitentan is a new oral dual (ETA and ETB) Endothelin Receptor Antagonist (ERA). Recently, the phase III SERAPHIN trial enrolled a total of 742 patients comparing placebo to Macitentan 3 mg and Macitentan 10 mg in a long-term trial. It is the largest PAH prospective

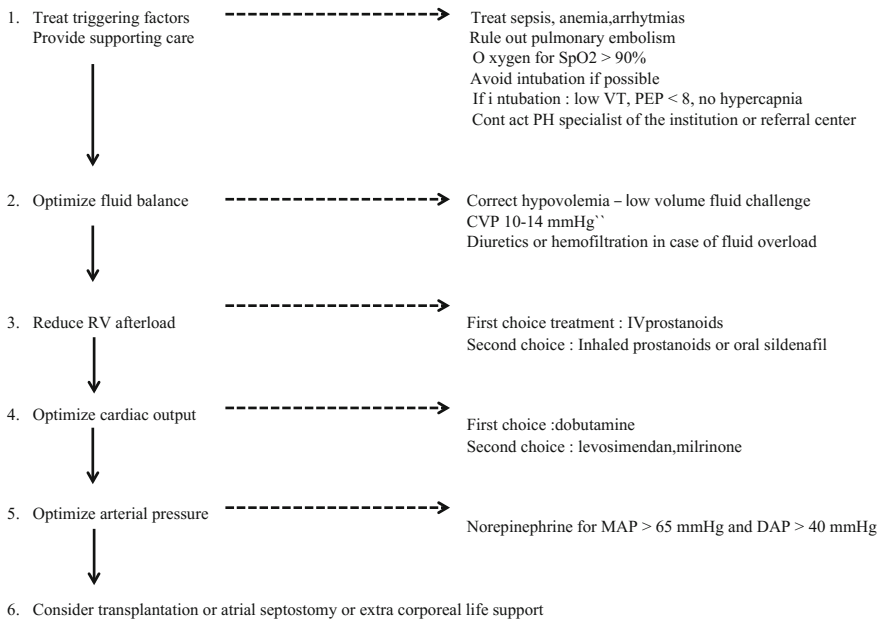

Fig. 3 General approach of decompensated PAH in ICU patients. Adapted from [15]. *CVP* central venous pressure, *VT* tidal volume, *IV* intravenous, *PEP* positive expiratory pressure, *MAP* mean arterial pressure, *DAP* diastolic arterial pressure

study to date. In this study, Macitentan significantly reduced morbidity and mortality among patients with pulmonary arterial hypertension [28].

In the Context of ICU (Fig. 3)

The main objective is to prevent and to treat RV failure. The principles are reduction of PVR by vasodilators, limitation of pulmonary hypoxic vasoconstriction by oxygen, preservation of coronary output by control of systemic arterial pressure, use of inotropes, arrhythmia control. No algorithm was validated in ICU patients. Each therapeutic option must be individually tested. Anemia should be treated (>10 g/dL).

Mechanical ventilation may be deleterious since it can increase PVR. High levels of PEP (positive expiratory pressure) also increase PVR, RV afterload and PAP. On the opposite, hypercapnia may induce a 50 % increase of PVR. If the patient is intubated, mechanical ventilation adjustments are crucial but difficult. The principles are that low levels of tidal volume and PEP (3–8 cm H2O) are necessary whereas hyperpania should not be tolerated

Hypovolemia should not be tolerated but volemia assessment is difficult in this context. Evaluation of fluid responsiveness by fluid challenge with low fluid

Table 8 Recommendations for efficacy of specific drug therapy, balloon atrial septostomy, and lung transplantation for pulmonary arterial hypertension (class 1) according to WHO functional class. Adapted from [5]

Measure/treatment	Classes of recommendation–level of evidence		
	WHO-FC II	WHO-FC III	WHO-FC IV
Calcium channel blockers	I–C[a]	I–C[a]	–
Endothelin receptor antagonists (ERA)			
Ambrisentan	I–A	I–A	IIa–C
Bosentan	I–A	I–A	IIa–C
Sitaxentan[b]	IIa–C	I–A	IIa–C
Macitentan—promising results in PAH and thromboembolic PH	No actual recommendation		
Phosphodiesterase type-5 inhibitors			
Sildenafil	I–A	I–A	IIa–C
Tadalafil	I–B	I–B	IIa–C
Prostanoids			
Beraprost	–	IIb–B	–
Epoprostenol (intravenous)	–	I–A	I–A
Iloprost (inhaled)	–	I–A	IIa–C
Iloprost (intravenous)	–	IIa–C	IIa–C
Treprostinil (subcutaneous)	–	I–B	IIa–C
Treprostinil (intravenous)	–	IIa–C	IIa–C
Treprostinil (inhaled)	–	I–B	IIa–C
Soluble guanylate cyclase stimulator			
Riociguat—promising results in PAH	No actual recommendation		
Initial drugs combination therapy	–	–	IIa–C
Sequential drugs combination therapy	IIa–C	IIa–B	IIa–B
Balloon atrial septostomy	–	I–C	I–C
Lung transplantation	–	I–C	I–C

[a] Only for positive vasoreacivity test
[b] Sitaxentan was withdrawn on 2010 due to severe unpredictable side effects (hepatic toxicity)

volume is logical but not demonstrated. Dynamic indices cannot be used in case of PH [29]. The optimal value for central venous pressure is 10–14 mm Hg [30].

In order to maintain cardiac output, the concomitant use of vasopressors and inotropes are frequently necessary. Dobutamine is the most inotrope studied in PH. Low doses (5 mcg/Kg/min) decrease PVR and PAP and moderately increase cardiac output. Higher doses are not recommended as they induce tachycardia without decreasing RVP. Systemic vasodilation is frequently observed in decompensated PH, due to systemic inflammatory response syndrome. This phenomenon can be worsened by sepsis. Systemic vasodilation is characterized by low diastolic pressure, which is the main determinant of coronary pressure. Therefore, a low diastolic pressure (>40–50 mm Hg) [31] may induce functional myocardial ischemia that may worsen RV function. In this case, Norepinephrine is the agent of choice since it induces systemic vasoconstriction without alteration of coronary

Table 9 Pulmonary vasodilators that may reduce PVR in ICU setting. Adapted from [14]

Drug	Dose	Duration of action	Side effects
Intravenous			
Prostacyclin (Epoprostenol, Flolan®)	Start at 1 ng/kg/min 2-ng/kg/min increments according to effect	3–5 min	Systemic hypotension, worsening oxygenation, antiplatelet effect, headache, flushing, nausea, diarrhea
Iloprost	1–5 ng/kg/min	30 min	Idem Flolan
Inhaled			
Prostacyclin (Epoprostenol, Flolan®)	0.2–0.3 ml/min of 10–20 μg/ml nebulized into inspiratory limb of ventilator circuit (30–40 ng/kg/min)	3–5 min	Less hypotension, better oxygenation
Iloprost	2.5–5 μg 6–9 times/day, 1 mg/ml into the ventilator circuit or via face mask at 0.2–0.3 ml/min for 10–20 min	30 min	As above, plus bronchospasm
NO	5–80 ppm, continuously	15–30 s	Methemoglobinemia
Oral			
Sidenafil	0.25–0.75 mg/kg/4 h	3–4 h	Few hypotension Few paradoxical hypoxia

blood flow. The objective of MAP is classical, 65–75 mm Hg [32]. Levosimendan can be used but may be individually tested as there is a risk of systemic hypotension. Intravenous milrinone has limited indications because of hypotension.

The use of selective pulmonary vasodilators in order to decrease RV afterload is logical in decompensated PAH [14]. The agents that can be used, their dose, duration of action and side effects are summarized in Table 9.

Endothelin receptor antagonist has not been tested in the context of ICU. Intravenous administration can induce severe hypotension that limits their use in unstable patients.

Inhaled NO decreases PAP and increases RV performance at a dose ranging from 5 to 40 ppm. It has some limitations: rebound effect, methemoglobinemia, and price. Moreover, the beneficial effect is not sustained by 72 h in ARDS patients [33]. This diminution in the beneficial effect of NOi may be due to the fact that NO also has proinflammatory activityand prolonged exposure can result in oxidative injury and the nitrosylation of proteins. To date, at our knowledge, no long term evaluation of NOi was performed for PAH patient.

Inhaled epoprostenol (Flolan®) induces significant pulmonary vasodilation without systemic effect. Continuous infusion of epoprostenol via an automatic syringe in a nebulization device at a dose of 12.5–50 ng/Kg/min in the inspiratory circuit or mask is feasible. Intravenous epoprostenol is started at the dose of 1 ng/

kg/min and titrated upward in 2 ng/kg/min increments according to clinical effect. The use of intravenous forms of prostanoids is limited in ICU since they have severe systemic effects: hypotension, paradoxical worsening oxygenation, nausea, headache, flush, diarrhea, antiplatelet effects.

Intravenous ilomedin (Iloprost®) has been used in post-operative ICU patient at a dose of 2 $\mu g.kg^{-1}$ over 20 min. Its efficacy and side effects are comparable to epoprostenol. One study suggest short duration of hemodynamic effects (20 min) limiting its use [34], whereas one other found sustained effect other 2 h but in ARDS patients [35]. A recent study in eight patients with PAH functional class IV with right heart failure, four of them candidates for lung transplantation, suggest the association inhaled Iloprost plus oral Sildenafil as an alternative to Epoprostenol [36].

The use of sildenafil was reported as efficacious in ICU patients in several case reports at a dose of 25–50 mg followed by 25 mg/8 h. The effects are seen after 15 min of oral intake and the peak efficacy is observed between 30 and 60 min. Intravenous Sildenafil administered at infusion rate of 2 and 9 mg/h for 20 min each to achieve plasma levels of 100 and 300 ng/l respectively (equivalent to peak plasma levels of 25 and 50 mg of oral sildenafil therapy) led to significant reductions in mPAP (−7.4 mm Hg or—16.9 % (9.2) p <0,001) and PVR (−188.8 dyn/s/cm^5 or—25.1 % (11.4) p <0,001) [37].

The treatment of the cause of acute exacerbation is fundamental, especially sepsis. In case of failure of medical treatment, septostomy, extra corporeal life support and transplantation should be discussed with referral center only in a highly selected population since the mortality is very high in this context.

Conclusion

The prognosis of PAH was consistently improved in the ten past years by introduction of selective pulmonary vasodilators and management by highly specialized medical teams. In ICU patients, PAH remains a severe disease with a high mortality rate. When PAH is suspected, a systematic diagnosis approach is of particular importance in order to rapidly eliminate left cardiac, thromboembolic and pulmonary causes of PH. Left cardiac disease is the most common cause of PH. Early recognition of PAH allows a rapid introduction of selective pulmonary vasodilators that can improve outcome. Idiopathic PAH is the most frequent cause but it can also be associated with scleroderma, HIV infection, anorexigen toxicity, thyroid disease, cirrhosis. Pulmonary vasodilators should be only a part of a general management including treatment of triggering factors, optimization of fluid balance, decrease of RV afterload by using pulmonary vasodilators while maintaining cardiac output and mean arterial pressure. The early contact of PH referral center or specialized physician is of particular importance.

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