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Rehabilitation in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: results from the Grenoble experience

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UNIVERSITÉ GRENOBLE ALPES
UFR DE MÉDECINE DE GRENOBLE

Année : 2019

LA READAPTATION CARDIAQUE DANS LA PRISE EN CHARGE DE
L'HYPERTENSION ARTERIELLE PULMONAIRE ET DE L'HYPERTENSION
PULMONAIRE THROMBOEMBOLIQUE CHRONIQUE : RÉSULTATS DE
L'EXPÉRIENCE GRENOBLOISE

THÈSE

PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE
DIPLOME D'ÉTAT

Thomas BARRET

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE GRENOBLE

Le 25 Novembre 2019

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PART I:
**PULMONARY ARTERIAL HYPERTENSION, CHRONIC
THROMBOEMBOLIC PULMONARY HYPERTENSION AND
REHABILITATION: A REVIEW**

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ABBREVIATIONS

6MWD, six-minute walk distance

6MWT, six-minute walking test

ALK1, activin receptor-like kinase 1

BMPRII, bone morphogenetic protein receptor type II

BNP, brain natriuretic peptide

BPA, balloon pulmonary angioplasty

CPA, conventional pulmonary angiography

CTEPH, chronic thromboembolic pulmonary hypertension

CTPA, computed tomography pulmonary angiography

ENG, endoglin 1

ERA, endothelin receptor antagonist

ERS, european respiratory society

ESC, european society of cardiology

ET, exercise training

FC, functional class

HIV, human immunodeficiency virus

HR, heart rate

IPAH, idiopathic pulmonary arterial hypertension

LVEF, left ventricular ejection fraction

mPAP, mean pulmonary artery pressure

MRI, magnetic resonance imaging

PAH, pulmonary arterial hypertension

PAWP, pulmonary arterial wedge pressure

PAOP, pulmonary arterial occlusion pressure

PCH, pulmonary capillary haemangiomas

PDE5, phosphodiesterase-5

PEA, pulmonary endarterectomy
PH, pulmonary hypertension
PVOD, pulmonary veno-occlusive disease
PVR, pulmonary vascular resistance
RAP, right atrial pressure
RCTs, randomized control trials
SF-36, Short Form 36
sGC, soluble guanylate cyclase
SMAD9, Mothers against decapentaplegic homolog 9
UK, United Kingdom
USA, United States of America
WHO, World Health Organization
WSPH, World Symposium on Pulmonary Hypertension
WU, Wood units

1. Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are subtypes of pre-capillary pulmonary hypertension (PH). In these conditions, remodeling of the pulmonary vascular bed with an obliterative vasculopathy is responsible for the rise in pulmonary arterial pressure and pulmonary vascular resistance (PVR), and without treatment ultimately leads to right ventricular failure and death. Despite advances in drug therapy with improvements in the short-term survival of patients with PAH, the condition remains incurable. The recent development of effective medical therapies and the use of combination therapy have considerably improved the prognosis of patients, but also functional capacity and haemodynamics. By contrast, CTEPH is potentially curable.

For decades, exercise training has not been recommended for patients with pulmonary arterial hypertension (PAH) due to the fear of a possible risk of sudden cardiac death, arising from worsening hemodynamics and deterioration in right heart function during exercise. It was commonly believed that physical training may contribute negatively to the evolution and progression of PH (1).

Because of a lack of efficacy data, supervised exercise rehabilitation was first recommended from 2009 ESC/ERS pulmonary hypertension Guidelines but only in deconditioned PAH patients in a highly supervised setting with avoidance of excessive physical activity (exercise training (ET) remained in class IIa recommendation with a level of evidence B) (2). And yet, reduced exercise capacity in PH is common and associated with anxiety disorders, depression, skeletal muscle dysfunction and compromised quality of life (3,4).

Since then, more studies in rather small cohorts of patients with PAH and CTEPH have shown beneficial effects of exercise training as add-on to medical therapy by improving symptoms, exercise capacity and quality of life, with reassuring data on safety (5–8).

2. Definition of pulmonary hypertension

Normal mean pulmonary artery pressure (mPAP) at rest is 14.0 ± 3.3 mmHg; this value is slightly influenced by age and posture, and independent of sex and ethnicity (9)

Since the 1st World Symposium on Pulmonary Hypertension (WSPH) organised by the WHO in 1973, pulmonary hypertension is defined by a resting mPAP ≥ 25 mm Hg measured by right heart catheterisation in the supine position (10–12).

During the 6th WSPH in 2018, the task force members suggested mPAP > 20 mmHg as above the upper limit of normal (above the 97.5th percentile), and the need for PVR ≥ 3 WU to define the presence of pre-capillary PH (groups 1, 3 and 4, some patients from group 5, and exceptionally patients from group 2 with combined pre- and post-capillary PH) (13).

3. Different groups of pulmonary hypertension

PH is classified into five groups based on the aetiology, or pathophysiological features:

- Group 1, pulmonary arterial hypertension (PAH) comprises patients with precapillary pulmonary hypertension due to distinct underlying disorders who share a similar angioproliferative vasculopathy in the pulmonary arterioles, leading to endothelial and smooth muscle proliferation and dysfunction, inflammation and thrombosis (14,15). PAH comprises various different pathologies, such as idiopathic, heritable, drug-induced PAH (e.g. anorexigenic agents), as well as PAH associated with concomitant diseases such as connective tissue disease, HIV infection, portal hypertension, or congenital heart disease. Since the 3rd WSPH held in 2003, pre-capillary PH of group 1 (PAH) has been defined by the presence of mPAP ≥ 25 mmHg with a normal pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and elevated pulmonary vascular resistance (PVR) ≥ 3 Wood Units (WU) and the absence of other causes of pre-capillary PH, (e.g. hypoxemia or chronic parenchymal lung diseases or chronic thromboembolic disease) (10,11).
- Group 2 is classified as pulmonary hypertension due to left heart disease.
- Group 3 includes PH due to lung diseases and/or hypoxia.
- Group 4 includes those with PH due to pulmonary artery obstructions, such as chronic thromboembolic PH.
- Group 5 is pulmonary hypertension due to miscellaneous disorders that cannot be attributed to one other group (for example pulmonary hypertension in the context of haematological disorders).

Figure 1: Clinical classification of pulmonary hypertension updated from Simonneau et al. (13)

1: PAH

- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with:
 - 1.4.1 Connective tissue disease
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart disease
 - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

2: PH due to left heart disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3: PH due to lung diseases and/or hypoxia

- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4: PH due to pulmonary artery obstructions

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5: PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

4. Epidemiologic data

Because the diagnosis requires an invasive procedure (right heart catheterization), the epidemiology of pulmonary hypertension is difficult to study. Therefore, large-scale population studies are based on echocardiography because invasive tests for epidemiological studies would not be ethical.

a. PAH

The reported incidence of pulmonary arterial hypertension in the developed world is 1,1–7,6 per million adults per year; the prevalence of pulmonary arterial hypertension is 6,6–26,0 per million adults (16–19)

Pulmonary arterial hypertension has been thought to affect mainly younger people, mostly females (20). This consideration is particularly true for heritable PAH, which affects twice as many women as men (21) and the average age at the time of diagnosis was approximately 50 years (22).

More recently, in Germany the average age of patients at the time of diagnosis was 64 years (22), and in UK 29% of the patients with newly diagnosed PAH were over the age of 70 years (23); reinforcing the notion that the phenotype and the age of patients with PAH were continuous to change. Advancing age has been identified as an independent risk factor for mortality in this population (24).

b. CTEPH

In the various registries, CTEPH is mostly diagnosed between 50 and 70 years-old, with males and females being equally affected (25–27).

Studies determined that the incidence of CTEPH was 1,0–8,8% of all survivors of acute pulmonary embolism (28–31), with a calculated average incidence of 4% in Europe and USA (32).

In European registries, the reported annual chronic thromboembolic pulmonary hypertension incidence rates is 0,9-5,7 cases per million adults per year (16,19,33,34). But this number is much fewer than the expected annual incidence (16).

Up to 25% of patients with CTEPH have no history of acute pulmonary embolism (35), the symptoms are relatively unspecific, and physicians are ill-informed about the disease; this is why CTEPH is certainly underdiagnosed (36). The calculated incidence including diagnosed and undiagnosed disease ranges from 30 to 50 cases per million inhabitants per year in the USA and Europe. The projection model indicated that incidence of CTEPH will continue to increase over the next decade (37).

5. Risks factors

a. PAH

The idiopathic form of the disease concerns mostly women of childbearing age. There is an inherited form of PAH. Several gene mutations have been identified; the most common coding for bone morphogenetic protein receptor type II (BMPR2) cause up to 80% of the heritable PAH population (despite an incomplete penetrance about 20%), and 20% of cases of sporadic idiopathic disease (38,39). In comparison, activin receptor-like kinase 1 (ALK1), mothers against decapentaplegic homolog 9 (SMAD9) and endoglin 1 (ENG) concern only 5% of cases of heritable disease (15).

Lupus, scleroderma, cirrhosis, and HIV infection are strongly associated with PAH. Some drugs, methamphetamine and cocaine use increase the risk for developing this disease (40).

b. CTEPH

Multiple risk factors have been linked to CTEPH, such as prior splenectomy, autoimmune or hematological disorders (e.g., lupus or antiphospholipid syndrome), cancer, ventriculoatrial shunts, chronic inflammatory disorders (such as osteomyelitis and Crohn's disease), thyroid replacement therapy, and non-O blood group (41–45).

The higher incidence of chronic thromboembolic disease in Japanese patients compared with patients from USA, and the predominance of CTEPH among women, suggest that race, sex, or environmental exposure may play a key role in this condition (46).

6. Pathophysiology

Pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH) share similar physiological outcome, in which remodelling of the pulmonary vascular bed is responsible for the rise in pulmonary vascular resistance (PVR), leading to progressive right ventricular failure and functional decline.

a. PAH

The pathobiology of PAH is complex and incompletely understood. Latest advances have led to a better understanding of the key components underlying this inadequate accumulation of pulmonary vascular cells within the arterial walls leading to vascular remodeling causing a partial occlusion of small pulmonary arteries, and high pulmonary arterial pressure (15).

Among the underlying molecular and cellular mechanisms, some play critical roles in the pathogenesis of the disease (47,48) :

- **pulmonary endothelial dysfunction**, in particular vascular stiffness (by increased wall thickness, smooth muscle cells proliferation and changes in the type and quantity of extracellular matrix proteins (49)), and endothelial-to-mesenchymal transition (involved by the formation of neo-intimal vascular lesions in the pulmonary arteries caused by increased proliferation of endothelial cells (EC) and smooth muscle cells (SMC) (50)).
- **alterations of the inter-cell communications within the pulmonary arterial walls**,
- **alteration of the inflammatory component**: vascular cells can respond to inflammatory stimuli by enhanced proliferation and migration and reduced apoptosis; responsible for the exaggerated perivascular infiltration of inflammatory cells (B- and T-lymphocytes, mast cells, dendritic cells, macrophages, etc.) (51).
- **loss of BMPR2** (bone morphogenic protein receptor type 2) **activity** increases apoptosis in vascular cells, leading to vascular remodeling and ultimately PAH (15,52)

However, there are many other complex and often interacting pathways involved in the development of PAH.

b. CTEPH

The pathophysiology of CTEPH is complex and multifactorial; including pulmonary artery obstruction by non-resolved thrombi, and pulmonary microvasculopathy. But it remains still not completely understood.

The following factors have been related to failure of thrombus resolution, and development of CTEPH: inflammation; genetic factors leading to fibrinolysis resistance; reduced fibrinolytic capacity; increased hypercoagulability; impaired angiogenesis; small vessel disease (53,54).

7. Clinical presentation

The cardinal symptom of PH is progressive exercise dyspnea (11); but symptoms of PH remain non-specific: dyspnea upon exertion, fatigue, weakness, chest pain, lightheadedness/syncope with exertion, anorexia and, less frequently, cough. Progressive right-sided heart failure occurs in late stage of disease. Rarely, haemoptysis, hoarseness (unilateral vocal chord paralysis) and arrhythmias may characterise PH (55).

Physical examination is often without abnormalities, when PH is compensated. Findings may include loud heart sound (P2 component), murmur of tricuspid regurgitation, and signs of right-sided heart failure as jugular venous distension, hepatojugular reflux, ascites, hepatomegaly and splenomegaly, peripheral oedema (55). In some cases, clinical examination may suggest an underlying cause of PH.

Regarding CTEPH, about 25% of patients have no history of acute pulmonary embolism (35), and there are no specific symptoms of CTEPH. For this reason, CTEPH diagnosis is often delayed : mean delay from onset of symptoms to diagnosis of CTEPH was 18 ± 26 months (56). Thus, patients may be asymptomatic for several years before presenting progressive dyspnoea on exertion, exercise intolerance, fatigue or depression (56) ; then syncope and oedema occurs in late stages of disease progression. (36).

8. Diagnosis

In the case of clinical suspicion of pulmonary hypertension, an echocardiography is performed in search of elevation of peak tricuspid regurgitation velocity over 3.4m/s or over 2.8m/s associated with right heart overload. But to confirm the diagnosis of pulmonary hypertension right heart catheterisation is mandatory. Diagnostic criteria for PAH and CTEPH include a resting mean pulmonary arterial pressure greater than or equal to 25 mmHg. Measurement of pulmonary arterial occlusion pressure (PAOP) is necessary to exclude post-capillary pulmonary hypertension.

a. PAH

In case of PH suspicion, the diagnosis process have to rule out all other causes of PH, in particular most common clinical groups of PH [group 2 and group 3], then distinguishes group 4, and finally concluded the PAH's accountability (26).

Indeed, if transthoracic echocardiography is compatible with PH, the clinician needs to collect clinical history, symptoms, physical signs, ECG, chest radiograph, pulmonary function tests and chest CT to identify the presence of group 2 (left heart diseases) or group 3 (lung diseases) PH. If the diagnosis of left heart or lung diseases is confirmed, the appropriate treatment for these illnesses should be considered.

In the contrary case, a V/Q lung scan should be performed for the differential diagnosis between CTEPH and PAH.

b. CTEPH

Even though there is no clear recommendation, a screening by echocardiography could be considered up to 2 years after acute pulmonary embolism (46).

CTEPH is defined as symptomatic pulmonary hypertension with persistent pulmonary perfusion defects despite a 3-month anticoagulant therapy (37).

Imaging plays a central role in CTEPH diagnosis: ventilation/perfusion lung scintigraphy (V/Q scan) shows segmental perfusion defects without matching ventilation abnormalities. Thereafter presence of specific imaging findings on computed tomography pulmonary angiography (CTPA), cardiovascular magnetic resonance imaging (MRI) or conventional pulmonary angiography (CPA) will define the diagnosis of CTEPH (26,57)

9. Treatment

a. PAH

Treatment includes supportive therapies (as anticoagulants when indicated, diuretics, supplemental oxygen, psychosocial support, genetic counselling, appropriate birth control,

supervised physical exercise) (15,26), and disease-targeted drugs, consisting of vasodilators agents (5).

Until 2001, epoprostenol was the only medication available to treat PAH, and mainly used as a bridge to transplantation (58).

The pathogenesis of PAH involves dysfunction of three key pathways: the nitric oxide pathway, the prostacyclin pathway, and the endothelin pathway (59), cf. annex 1.

These three relevant signaling pathways represent therapeutic targets for the medical treatment options (60), with several drugs currently approved for the treatment of pulmonary arterial hypertension (61):

- the endothelin receptor antagonists ambrisentan, bosentan, and macitentan;
- the phosphodiesterase-5 inhibitors sildenafil and tadalafil;
- the soluble guanylate cyclase stimulator riociguat;
- the prostacyclin analogues beraprost (in Japan and South Korea only), epoprostenol, iloprost and treprostinil;
- the prostacyclin receptor agonist selexipag.

Adverse effects occur with all of the specific medication (59).

Over the past few decades, the development of effective medical drugs and the use of combination therapy to target multiple pathogenic pathways simultaneously have considerably improved the prognosis of patients with PAH (62), and also improved symptoms, exercise capacity, and quality of life (66).

Whereas previous guidelines recommended initial monotherapy, followed by regular assessments, and initiation of combination therapy when treatment goals were not met (61), the current ESC/ERS guidelines recommend initial combination therapy:

- Newly diagnosed PAH patients with low or intermediate risk receive initial or early combination therapy comprising an endothelin receptor antagonist (ERA) with a phosphodiesterase-5 (PDE5) inhibitor or a soluble guanylate cyclase (sGC) stimulator (63–65).
- High-risk PAH patients receive a recommended triple treatment with an ERA, a PDE5 inhibitor or an sGC stimulator, and an intravenously administered prostacyclin analog (26).

The treatment response and clinical assessment must be performed every 3-6 months (26). The treatment strategy depends on the individual response: if the patient has not achieved the primary treatment goal, that is attainment of the low-risk category after the initial treatment, the next step is dual or triple combination therapy (11).

Sitbon and al. showed that initial oral dual combination therapy of an ERA plus a PDE5 inhibitor was associated with significant improvements in functional class, exercise capacity and dyspnea (58). Simultaneously, signs of right heart failure and levels of brain natriuretic peptide (BNP) were significantly reduced, suggesting a reduction in clinical worsening. This strategy was also accompanied by significant improvements in 6MWD and haemodynamic parameters, including reductions in pulmonary vascular resistance (PVR) and mPAP.

In patients with severe PAH, the triple combination therapy is a way to improve the long-term benefits (66).

Despite the currently available treatment, many patients remain symptomatic with reduced exercise capacity, quality of life, or develop right heart failure (67).

Current specific PAH therapy do not specifically target inflammation and pulmonary vascular remodeling, which are likely new targets of the next therapeutic innovation. It requires a better identification of the pathobiological mechanisms underlying,

b. CTEPH

Surgical pulmonary endarterectomy is the treatment of choice for patients with chronic thromboembolic pulmonary hypertension (26). Among them 50 to 70% are operable (35). The perioperative mortality at experienced centres is 2 to 4% (68,69). Approximately half of the patients had a post-operative mPAP ≤ 25 mmHg (69). In around 20% of patients treated surgically, the residual pulmonary hypertension is clinically significant and has to be treated (69).

For patients who are not candidates for surgery, interventional balloon pulmonary-angioplasty is an emerging treatment option to recanalize obliterated pulmonary vessels at subsegmental level (25).

Riociguat is the only drug approved for patients with inoperable chronic thromboembolic pulmonary hypertension or residual postoperative disease. Other classes of drugs might be used with a lower grade of recommendation. (61)

10. Prognosis and risk assessment

PH is characterized by a progressive increase in pulmonary vascular resistance, leading to right heart failure and premature death (70,71).

a. PAH

Over the past decades, the life expectancy of PAH patients has increased with a 3-year survival rate of 70 to 80% now (24), compared with 40% in the 1980s (11). Before the late 1990s, treatments for PAH patients consisted of supportive therapy, and was focused on symptoms related to right heart failure, with a median survival of 2.8 years in 1986 (95% CI, 1.9 to 3.7 years) (72). Recent data from the United States-based registry assessing pulmonary arterial hypertension disease management (REVEAL registry) showed a median survival of 7 years presumably due to a combination of significant advances in treatment strategies and patient support strategies (15,62). Despite improvements in the short-term survival of patients with PAH, the condition remains incurable (26).

The 2015 ESC/ERS (European Society of Cardiology/European Respiratory Society) guidelines (26) and the 2018 Proceedings of the 6th World Symposium on Pulmonary Hypertension (73) recommend regular risk assessment at expert PH centres using a series of variables to stratify patients into low, intermediate and high-risk categories (corresponding to an estimated one-year mortality rate of <5%, 5–10% and >10% respectively), *cf Annex 2*. This assessment is meant to be applicable in patients with newly diagnosed PAH and at any time during the course of the disease, and aims to facilitate treatment decisions. It includes clinical features (e.g. World Health Organization (WHO) functional class (FC), right ventricular function), exercise testing (e.g., 6-minute walking test (6MWT), cardiopulmonary exercise testing), imaging (echocardiography, cardiac magnetic resonance imaging), haemodynamics (right atrial pressure, cardiac index, mixed venous oxygen saturation), and biomarkers (BNP and NT-proBNP).

According to these guidelines, certain low-risk features are associated with better prognosis in PAH, such as no sign right heart failure, a WHO FC I or II, a 6MWD >440 m, an haemodynamic assessment with a right atrial pressure (RAP) <8 mmHg and a cardiac index ≥ 2.5 L/min/m². Also, BNP levels <50 ng/L or NT-proBNP <300 ng/L are considered to be low-risk features.

During follow-up, achieving and maintaining a low-risk profile is the recommended goal of PAH treatment. However, the accuracy of this risk assessment has not been fully established and most of cutoffs are based on expert opinion, with low levels of evidence.

Since then, abbreviated versions of the 2015 ESC/ERS risk stratification strategy have been evaluated retrospectively in newly diagnosed PAH (74–77):

- Boucly et al. (2017) studied a retrospective incident cohort of patients with PAH, and showed the risk of death or lung transplantation was accurately determined using a simple quantification of the number of low-risk criteria present at diagnosis, and, most importantly, achieved during the first year of follow-up for WHO FC, 6MWD, right atrial pressure (RAP) and cardiac index. In the analysis, attaining only two or less low-risk criteria at follow-up had a worse long-term prognosis than those with three or four low-risk criteria (74).
- Kylhammar et al. (2017) proposed a method whereby 8 criteria (6MWD, WHO FC, NT-proBNP, right atrial area, pericardial effusion, RAP, cardiac index, and SvO₂) are graded from 1 to 3 (1=low, 3=high) using the ESC/ERS risk stratification. The rounded mean of these grades is then used to define patient risk status (76).
- Hoeper et al. (2017) evaluated an abbreviated version of the risk stratification model in newly diagnosed PAH patients (from the COMPERA web-based PH registry) using 6 variables (6MWD, WHO FC, NT-proBNP/BNP, RAP, cardiac index, and SvO₂) and the same analysis method as Kylhammar et al. Among them, 6MWD, WHO FC, BNP/NT-proBNP and SvO₂ were closely linked to the mortality risk (75).

Two studies in PH have demonstrated that the presence of anaemia is indicative of a poor prognosis (78,79). Furthermore, iron deficiency is prevalent in patients with IPAH and is associated with disease severity (80,81).

b. CTEPH

Unlike others forms of PH, CTEPH is potentially curable. Pulmonary endarterectomy (PEA) is the treatment choice for patients who are surgical candidates (82) : however, up to 50% of patients are considered inoperable because of an inaccessible and/or distal thromboembolism, or serious comorbidities (34).

31% to 50% develop persistent/recurrent pulmonary hypertension after undergoing PEA (77,82). More recently, balloon pulmonary angioplasty (BPA) may be considered in patients who are technically non-operable or carry an unfavourable risk/benefit ratio for PEA (26).

However, without surgical intervention survival is poor and proportional to the degree of pulmonary hypertension and right ventricular dysfunction: in 1982, CTEPH patients had an estimated 5-year survival of 30% if mPAP was greater than 40 mmHg, and 10% if mPAP was more than 50 mmHg (83).

With new treatment options, including BPA, the prognosis of non-operated patients with CTEPH improved. Indeed, recent studies estimate a 1-year survival over 90%, a 3-year survival of 85%, (84,85), and a 5-year survival around 60% (84).

In these patients, baseline NYHA FC, RAP, 6MWD, BPA therapy and diagnosis period (2006–2012 vs 2013–2016) were predictors of survival (85).

There is currently no established risk assessment strategy to guide treatment decisions in patients with CTEPH. However, a recent study suggested that that an abbreviated version of the ERS/ESC risk stratification may be applicable (with the method from Kylhammar et al.) to predict mortality in non-operated and medically treated CTEPH patients (84). In a similar way as PAH mortality risk, variables closely linked to the mortality risk were 6MWD, WHO FC, BNP/NT-proBNP.

11. Exercise training and pulmonary hypertension

a. Exercise training and rehabilitation

Chronic cardiorespiratory disorders as PAH lead to physical inactivity, skeletal muscle dysfunction and compromised quality of life (4). In addition, patients with PAH were advised, for decades, to avoid physical exercise which has been thought to carry a high risk of sudden cardiac death and exacerbate right heart failure. Indeed, it was commonly believed that physical activity may have a negative impact on patients by increasing pulmonary remodeling and contributing to the progression of PH (1). In PH population reduced exercise capacity is associated with depression and anxiety disorders (3).

In the guidelines of 2009, because of a lack of efficacy data, rehabilitation was considered only in special circumstances, such as in deconditioned PAH patients, in a highly supervised setting with avoidance of distressing and excessive physical activity (2).

However, there is some evidence from left heart failure that regular physical activity improve endothelial function, exercise capacity, and quality-of-life parameters, and may be beneficial even in severe disease (86). Physical training reduce vascular oxidative stress and exert beneficial vascular effects in part by increasing activity of endothelial nitric oxide synthase (87).

Since then, additional studies have been performed that provided evidence of improvements of symptoms and exercise performance with reassuring data on safety (6,7). However, it must be emphasised that the patients in these studies were all in a stable condition on advanced drug therapy, under close supervision in PAH expert centres and the training was specially designed for PAH patients.

In the updated guidelines of 2015 (26), specialised PAH rehabilitation is recommended for patients in stable clinical condition with the best standard of pharmacological treatment, with the notion that supervised rehabilitation should be implemented by centres experienced in both PAH patient care and rehabilitation of compromised patients (class IIa recommendation, evidence level B). Optimised pharmacological treatment is defined as single or combination therapy with PAH-targeted drug therapy such as calcium-channel blockers, prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and guanylate cyclase stimulator. The guidelines also clearly suggest that such an expert centre should consist of a multidisciplinary team including cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support. Furthermore, it is recommended for expert referral centres to have a direct link to adult congenital heart disease units, pulmonary endarterectomy surgeons and a lung transplantation programme. Expert referral centres are requested to follow at least 50 patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH), and should have two new referrals per months.

b. Mechanisms of exercise training in PAH patients

The exact pathophysiological mechanisms by which exercise leads to beneficial effects are not yet fully understood.

In mice, exercise training was able to prevent hypoxia-induced pulmonary vascular remodeling, and improved exercise capacity and pulmonary haemodynamics (88). The effect of exercise training on physical capacity was more important in mice who received drug treatment (sildenafil). The effects were not associated with changes in the expression of the nitric oxide, phosphodiesterase 5, or soluble guanylate cyclase pattern, which belongs to targeted pathways for PAH therapy. These results suggest that exercise training might be complementary to pharmacological treatment, affecting molecular pathways not yet identified.

In other rat and mice experiments, it has been shown an attenuation of acute vasoconstriction in response to hypoxia, a reduction in right ventricular pressure and pulmonary artery diameter, and a better right ventricle capillary density (89,90)

In patients with chronic heart failure and PAH, exercise training has been shown to reduce inflammation and TNF-level, which is involved in the development of PAH (91–93).

In PAH patients, skeletal muscle dysfunction has been reported with muscle atrophy, reduced capillary density, decreased oxidative enzyme activity, reduced exercise capacity and muscle strength, fewer type IIa fibres. In few studies, exercise training significantly improve these alterations in muscle tissue and muscle function (8,94,95).

Exercise training also improves lung performance with better pulmonary perfusion, oxygen uptake and inhibition of smooth muscle cells (95). In addition, it decreases insulin resistance that have been reported more prevalent in PAH population (96).

A recent study showed that aerobic exercise promotes a significant increase in H₂O₂/VEGF/p-Akt signal for pulmonary physiological angiogenesis (97).

In summary, exercise training impacts angiogenesis, muscular strength, right ventricle contractility, ventilatory efficiency, hormonal, and immune system, and may improve symptoms, exercise capacity, quality of life and hemodynamics.

C. Different components of the rehabilitation programme with pulmonary arterial hypertension (PAH)

Since 2006, several published studies conducted rehabilitation in PAH patients with different training protocols, but there is no consensus on how to train PH patients.

Most published studies were conducted in the PAH centre of Heidelberg in Germany (5,98): they established a training programme, which started as a 3-week inpatient training followed by a home-based training with individualised instructions and supervised by the respective expert centre. Before the rehabilitation and right after, patients are evaluated in the PAH centre and were stable and compensated under optimized medical therapy (such as endothelin antagonists, iloprost, sildenafil, calcium channel blockers, anticoagulants, diuretics, and supplemental oxygen) for at least 2-3 months before entering the study. The initial exercise training intensity was also assessed. During the following 3 weeks of in-hospital rehabilitation, the physicians for rehabilitation stay in contact with the PAH experts. The training consists of interval bicycle ergometer training with a lower workload (0 to 10W) for 30 seconds and a higher workload for 1 minute (20 to 35W) for 10 to 25 minutes per day in a supervised and monitored setting. The training intensity was increased (eg, up to 35 to 50 W) with respect to the individual tolerability and improvement. Training intensity was limited by peak heart rate (HR) (not more than 120 bpm), oxygen saturation (not less than 85%), and subjective physical exertion. If needed training was reduced. Furthermore, 60 minutes of walking, 30 minutes of dumbbell training of single muscle groups with low weights (500 to 1000 g) and 30 minutes of respiratory training were performed 5 days a week. Patients was also educated in perceiving their physical limits, and all patients were advised to avoid heavy exercise. Other centres have also used treadmill walking for 30 to 45 minutes under similarly intensive supervision (99).

And thus, most published studies used aerobic exercise training with low workload (intensity titrated between 40 to 80% of peak exercise capacity or about 60–80% of the HR achieved during a baseline exercise test) (95) under close supervision by PAH experts, in patients who were clinically stable and treated with optimized PAH drug therapy without signs of overt right heart failure.

d. Evidence and effects of rehabilitation in pulmonary hypertension patients

In healthy people and chronically ill patients, a higher daily physical activity lead to a better survival than less active controls (80,81).

Previous studies in rather small cohorts of patients with idiopathic pulmonary arterial hypertension (IPAH) and inoperable chronic thromboembolic pulmonary hypertension

(CTEPH) have shown beneficial effects of exercise training as add-on to disease targeted medical therapy by increasing exercise capacity and quality of life (5,8). The effects were observed in different forms of pulmonary vascular diseases, such as idiopathic PAH, CTEPH and PH due to respiratory or left heart diseases (7). The improvement in exercise capacity was recorded with an improvement in 6MWD, VO₂ peak, cardiac output (100), muscle strength and muscle endurance. Also, physical and mental quality of life scores measured with the SF-36 questionnaire improved significantly, especially in the domains of physical functioning, general health perception, vitality, social functioning, role emotional and mental health (6).

A meta-analysis in 2015, including 16 prospective intervention studies with 469 PH participants, observed a 53.3 m improvement in 6MWD at 15 weeks with exercise training on pooled analysis (weighted mean difference, 53.3 m; 95% CI, 39.5–67.2). Exercise training was also associated with significant improvement in pulmonary arterial systolic pressure (weighted mean difference, –3.7 mm Hg; 95% CI, –5.4 to –1.9), peak oxygen uptake (weighted mean difference, 1.8 mL/kg per minute; 95% CI, 1.4–2.3), and quality of life as measured on SF-36 questionnaire subscale scores. (99)

In 2017, a review of randomized controlled trials (RCTs) assesses the efficacy and safety of exercise-based rehabilitation for people with PH (most participants were Group I pulmonary artery hypertension) (101). They study 6 RCTs with 206 participants included. Study duration ranged from 3 to 15 weeks. Exercise programmes included both inpatient- and outpatient-based rehabilitation. The mean 6MWD following exercise training was 60.12 metres higher than control (30.17 to 90.07 metres, n = 165, 5 RCTs), the mean peak oxygen uptake was 2.4 ml/kg/minute higher (1.4 to 3.4 ml/kg/min, n = 145, 4 RCTs). The health-related quality of life also improved with a mean change for the SF-36 physical component score 4.63 points higher (0.80 to 8.47 points, n = 33, 2 RCTs) and for the SF-36 mental component score 4.17 points higher (0.01 to 8.34 points; n = 33; 2 RCTs).

Ehlken et al. (102) evaluated the effect of training on morbidity and mortality of PAH patients (n=58) compared with a retrospective control group (n=46) treated with usual care and optimized PAH therapy. During a mean follow-up of 24 ± 12 months, 25.8% of the patients receiving exercise training had adverse events, a rate much lower when compared to the control patients (54,4%). The incidence of clinical worsening was also lower. The 1- and 2-year survival rates were better in the exercise training group compared to the control group (100% and 95% vs. 93% and 88%, respectively; P<0.05).

e. Safety and adverse events

The rapid deterioration of right ventricle function leading to hemodynamic impairment, the occurrence of arrhythmias and syncope have been considered as the major risks of an exercise programme in patients with severe PAH (103,104).

Side effects in specialist centres under expert supervision were relatively rare. Actually, no study has reported an increased incidence of major adverse events in PAH patients undergoing a monitored and personalised exercise training (105)

Of the 6 RCTs analyzed by Morris et al., one study reported a single adverse event, where a participant stopped exercise training due to lightheadedness (101). In one of the largest studies (183 patients), a total of 13.6% of their participants had adverse events. Almost half of these patients suffered acute respiratory infections that had to be treated with antibiotics and forced the transitory suspension of the training programme. Severe adverse events, such as syncope/pre-syncope or supra-ventricular arrhythmias, occurred only in 4.4% of the patients. No signs of clinical worsening of right heart failure were detected during their hospitalisation, and no severe adverse episodes occurred when the patients continued the exercise training at home (between hospital discharge and the planned follow-up, 15 weeks later) (7). The meta-analysis including 16 prospective intervention studies with 469 PH patients, reported dizziness, presyncope, palpitation, hypotension and oxygen desaturation in 4,7% of training patients (one-third were not related to exercise). No major adverse events, such as progression of symptoms, right heart failure, or death, were observed among the patients during the training period. On median follow-up of 29.5 months (21–36 months), the survival rate was 91%, and the transplant-free survival rate was 89%. (99)

PH patients are often not aware of their own physical limits and may tend to overexercise. They have to be supervised and taught to recognise their physical limits, to prevent dangerous adverse effects of exercise. To minimize the risk, some safety precautions must be adopted when starting an exercise training programme. In the previous studies, it is required that PH patients are in clinically stable condition on optimised PH targeted therapy for at least 2 months (98). Training should be initiated with very low workloads (between 40 and 80% of peak exercise capacity), as well, dumbbell training must be practiced with low weights involving single muscle groups only. Oxygen saturation and heart rate have to be closely monitored (SpO₂ >85%, HR <120 per minute). Especially for severe patients, it is recommended to start the

rehabilitation programme in an inpatient setting, where both supervision during training and observation just after is possible (95).

f. Other components of rehabilitation

Patients with PH have to face many life stress factors, such as physical limitation, contraindications to have a pregnancy, high cost of treatment, unemployment, etc. Mental disorders (such as anxiety and depression) are more prevalent in this population, and closely related to the functional disability: the percentages of major depression higher in WHO FC IV patients (45%) than for the WHO FC I (7.7%) (3). That is why, goals of PH treatment should include quality of life as a major targets to reach (106), and many studies have pointed out that the rehabilitation programme, in addition to medical therapy, may improve depression and anxiety symptoms in patients with PH (5,105,107–110).

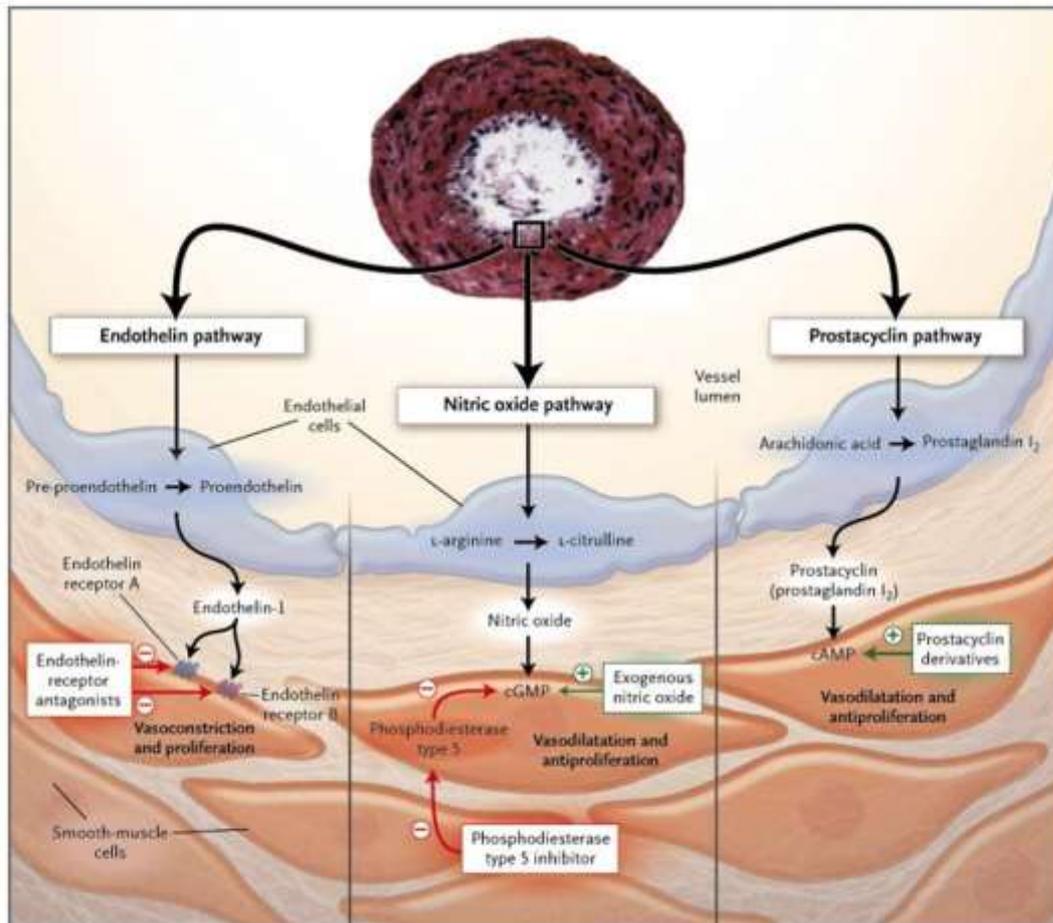
Rehabilitation is a global approach that not only consists of exercise training, but also includes a multidisciplinary team (including cardiology and respiratory medicine physicians, specialised nurses, radiologists, access to psychological and social work support), which provides informations, counselling and therapeutic interventions, during individual or small groups. It is a way to improve physical and emotional status. Moreover, during their stays patients may benefit from specific PH-drug titration: side effects are not uncommon, and could limit an increase in the dose if the titration is feared or not well tolerated by outpatients. A progressive titration when appropriate with management of side effects is a way to achieve optimal medical therapy.

12. Conclusions

Supervised rehabilitation in PH patients should be recommended, in addition to optimal medical treatment with PH targeted drugs, if performed in a highly experienced team under expert supervision. The pathomechanisms are not fully understood yet, but many studies agree in the favorable effects of training programme: it leads to significant improvements in symptoms, exercise capacity and quality of life.

This programme should be implemented by centres experienced in both PH patient care and rehabilitation. Some safety precautions must be adopted in order to avoid adverse events: among other things, patients have to be in stable condition on optimised medical therapy, and closely monitored during the exercise training. Despite the few studies so far, there is no published guidelines available detailing how exercise rehabilitation should be carried out.

ANNEXES



Annex 1 from Humbert et al. (59)

Determinants of prognosis* (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope ^b	Repeated syncope ^c
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO ₂ >15 ml/min/kg (>65% pred.) VE/VCO ₂ slope <36	Peak VO ₂ 11–15 ml/min/kg (35–65% pred.) VE/VCO ₂ slope 36–44.9	Peak VO ₂ <11 ml/min/kg (<35% pred.) VE/VCO ₂ slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm ² No pericardial effusion	RA area 18–26 cm ² No or minimal pericardial effusion	RA area >26 cm ² Pericardial effusion
Haemodynamics	RAP <8 mmHg CI >2.5 l/min/m ² SvO ₂ >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m ² SvO ₂ 60–65%	RAP >14 mmHg CI <2.0 l/min/m ² SvO ₂ <60%

Annex 2 from Galiè et al. (26)

BIBLIOGRAPHY

1. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet Lond Engl*. 1998 Aug 29;352(9129):719–25.
2. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2009 Oct;30(20):2493–537.
3. Löwe B, Gräfe K, Ufer C, Kroenke K, Grünig E, Herzog W, et al. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med*. 2004 Dec;66(6):831–6.
4. Osadnik CR, Rodrigues FMM, Camillo CA, Loeckx M, Janssens W, Doods C, et al. Principles of Rehabilitation and Reactivation. *Respiration*. 2015;89(1):2–11.
5. Mereles D, Ehlken N, Kreuzscher S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006 Oct 3;114(14):1482–9.
6. Grünig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, et al. Effect of Exercise and Respiratory Training on Clinical Progression and Survival in Patients with Severe Chronic Pulmonary Hypertension. *Respiration*. 2011;81(5):394–401.
7. Grünig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G, et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. *Eur Respir J*. 2012 Jul;40(1):84–92.
8. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJH, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2009 Sep 1;34(3):669–75.
9. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009 Oct;34(4):888–94.
10. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013 Dec 24;62(25 Suppl):D42-50.
11. M. Hoeper M, Ghofrani H-A, Grünig E, Klose H, Olschewski H, Rosenkranz S. Pulmonary Hypertension. *Dtsch Arztebl Int*. 2017 Feb;114(5):73–84.
12. Hatano S, Strasser T, Organization WH. Primary pulmonary hypertension: report on a WHO meeting, Geneva, 15-17 October 1973 [Internet]. World Health Organization; 1975 [cited 2019 Aug 26]. Available from: <https://apps.who.int/iris/handle/10665/39094>
13. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019 Jan;53(1):1801913.
14. Tuder RM, Archer SL, Dorfmueller P, Erzurum SC, Guignabert C, Michelakis E, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. *J Am Coll Cardiol*. 2013 Dec 24;62(25 Suppl):D4-12.
15. Lan NSH, Massam BD, Kulkarni SS, Lang CC. Pulmonary Arterial Hypertension: Pathophysiology and Treatment. *Diseases* [Internet]. 2018 May 16 [cited 2019 Oct 5];6(2). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023499/>
16. Hoeper MM, Humbert M, Souza R, Idrees M, Kawut SM, Sliwa-Hahnle K, et al. A global view of pulmonary hypertension. *Lancet Respir Med*. 2016;4(4):306–22.

17. Peacock AJ, Murphy NF, McMurray JJV, Caballero L, Stewart S. An epidemiological study of pulmonary arterial hypertension. *Eur Respir J*. 2007 Jul;30(1):104–9.
18. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med*. 2006 May 1;173(9):1023–30.
19. Escribano-Subias P, Blanco I, López-Meseguer M, Lopez-Guarch CJ, Roman A, Morales P, et al. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J*. 2012 Sep;40(3):596–603.
20. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med*. 1987 Aug;107(2):216–23.
21. Girerd B, Montani D, Eyries M, Yaici A, Sztrymf B, Coulet F, et al. Absence of influence of gender and BMPR2 mutation type on clinical phenotypes of pulmonary arterial hypertension. *Respir Res*. 2010 Jun 10;11:73.
22. Hoepfer MM, Huscher D, Pittrow D. Incidence and prevalence of pulmonary arterial hypertension in Germany. *Int J Cardiol*. 2016 Jan 15;203:612–3.
23. National Pulmonary Hypertension Audit - 2014 [Internet]. NHS Digital. [cited 2019 Aug 26]. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/national-pulmonary-hypertension-audit/national-pulmonary-hypertension-audit-2014>
24. Hoepfer MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol*. 2013 Sep 30;168(2):871–80.
25. Hoepfer MM, Madani MM, Nakanishi N, Meyer B, Cebotari S, Rubin LJ. Chronic thromboembolic pulmonary hypertension. *Lancet Respir Med*. 2014 Jul;2(7):573–82.
26. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016 Jan 1;37(1):67–119.
27. Ghofrani H-A, D'Armini AM, Grimminger F, Hoepfer MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013 Jul 25;369(4):319–29.
28. Dentali F, Donadini M, Gianni M, Bertolini A, Squizzato A, Venco A, et al. Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism. *Thromb Res*. 2009 Jul;124(3):256–8.
29. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Taliani MR, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. *Chest*. 2006 Jul;130(1):172–5.
30. Pengo V, Lensing AWA, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. 2004 May 27;350(22):2257–64.
31. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. *Circulation*. 1999 Mar 16;99(10):1325–30.
32. Opitz I, Ulrich S. Chronic thromboembolic pulmonary hypertension. *Swiss Med Wkly*. 2018 17;148:w14702.

33. Condliffe R, Kiely DG, Gibbs JSR, Corris PA, Peacock AJ, Jenkins DP, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2008 May 15;177(10):1122–7.
34. Kramm T, Wilkens H, Fuge J, Schäfers H-J, Guth S, Wiedenroth CB, et al. Incidence and characteristics of chronic thromboembolic pulmonary hypertension in Germany. *Clin Res Cardiol Off J Ger Card Soc.* 2018 Jul;107(7):548–53.
35. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. *Circulation.* 2011 Nov 1;124(18):1973–81.
36. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev.* 2017 Mar 31;26(143):160108.
37. Gall H, Hoeper MM, Richter MJ, Cacheris W, Hinzmann B, Mayer E. An epidemiological analysis of the burden of chronic thromboembolic pulmonary hypertension in the USA, Europe and Japan. *Eur Respir Rev Off J Eur Respir Soc.* 2017 Mar 31;26(143).
38. Larkin EK, Newman JH, Austin ED, Hemnes AR, Wheeler L, Robbins IM, et al. Longitudinal analysis casts doubt on the presence of genetic anticipation in heritable pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2012 Nov 1;186(9):892–6.
39. Soubrier F, Chung WK, Machado R, Grünig E, Aldred M, Geraci M, et al. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2013 Dec 24;62(25 Suppl):D13–21.
40. Pulmonary Arterial Hypertension Symptoms, Causes and Risk Factors [Internet]. American Lung Association. [cited 2019 Aug 31]. Available from: <https://www.lung.org/lung-health-and-diseases/lung-disease-lookup/pulmonary-arterial-hypertension/risks-symptoms-pul-arterial-hypertension.html>
41. Bonderman D, Jakowitsch J, Adlbrecht C, Schemper M, Kyrle PA, Schönauer V, et al. Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. *Thromb Haemost.* 2005 Mar;93(3):512–6.
42. Jaïs X, Ioos V, Jardim C, Sitbon O, Parent F, Hamid A, et al. Splenectomy and chronic thromboembolic pulmonary hypertension. *Thorax.* 2005 Dec;60(12):1031–4.
43. Bonderman D, Wilkens H, Wakounig S, Schäfers H-J, Jansa P, Lindner J, et al. Risk factors for chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2009 Feb;33(2):325–31.
44. Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev Off J Eur Respir Soc.* 2017 Mar 31;26(143).
45. Blauwet LA, Edwards WD, Tazelaar HD, McGregor CGA. Surgical pathology of pulmonary thromboendarterectomy: a study of 54 cases from 1990 to 2001. *Hum Pathol.* 2003 Dec;34(12):1290–8.
46. Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation.* 2011 Apr 26;123(16):1788–830.
47. Bordenave J, Tu L, Savale L, Huertas A, Humbert M, Guignabert C. Nouveau regard sur la physiopathologie de l'hypertension artérielle pulmonaire. *Rev Mal Respir.* 2019 Apr;36(4):433–7.
48. Hemnes AR, Humbert M. Pathobiology of pulmonary arterial hypertension: understanding the roads less travelled. *Eur Respir Rev Off J Eur Respir Soc.* 2017 Dec 31;26(146).
49. Hunter KS, Lammers SR, Shandas R. Pulmonary Vascular Stiffness: Measurement, Modeling, and Implications in Normal and Hypertensive Pulmonary Circulations. *Compr Physiol.* 2011 Jul;1(3):1413–35.

50. Hopper RK, Moonen J-RAJ, Diebold I, Cao A, Rhodes CJ, Tojais NF, et al. In Pulmonary Arterial Hypertension, Reduced BMP2 Promotes Endothelial-to-Mesenchymal Transition via HMGA1 and Its Target Slug. *Circulation*. 2016 May 3;133(18):1783–94.
51. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*. 2019 Jan;53(1).
52. Morrell NW, Adnot S, Archer SL, Dupuis J, Jones PL, MacLean MR, et al. Cellular and molecular basis of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009 Jun 30;54(1 Suppl):S20-31.
53. Yaoita N, Satoh K, Satoh T, Sugimura K, Tatebe S, Yamamoto S, et al. Thrombin-Activatable Fibrinolysis Inhibitor in Chronic Thromboembolic Pulmonary Hypertension. *Arterioscler Thromb Vasc Biol*. 2016;36(6):1293–301.
54. Robbins IM, Pugh ME, Hemnes AR. Update on chronic thromboembolic pulmonary hypertension. *Trends Cardiovasc Med*. 2017;27(1):29–37.
55. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of pulmonary hypertension. *Eur Respir J* [Internet]. 2019 Jan 24 [cited 2019 Aug 31];53(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6351333/>
56. Held M, Grün M, Holl R, Walter F, Schäfers H-J, Graeter T, et al. [Chronic thromboembolic pulmonary hypertension: Time delay from onset of symptoms to diagnosis and clinical condition at diagnosis]. *Dtsch Med Wochenschr* 1946. 2014 Aug;139(33):1647–52.
57. Nishiyama KH, Saboo SS, Tanabe Y, Jasinowodolinski D, Landay MJ, Kay FU. Chronic pulmonary embolism: diagnosis. *Cardiovasc Diagn Ther*. 2018 Jun;8(3):253–71.
58. Sitbon O, Sattler C, Bertoletti L, Savale L, Cottin V, Jaïs X, et al. Initial dual oral combination therapy in pulmonary arterial hypertension. *Eur Respir J*. 2016;47(6):1727–36.
59. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004 Sep 30;351(14):1425–36.
60. Rosenkranz S. Pulmonary hypertension: current diagnosis and treatment. *Clin Res Cardiol Off J Ger Card Soc*. 2007 Aug;96(8):527–41.
61. Hoeper MM, McLaughlin VV, Dalaan AMA, Satoh T, Galiè N. Treatment of pulmonary hypertension. *Lancet Respir Med*. 2016;4(4):323–36.
62. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest*. 2012 Aug;142(2):448–56.
63. Galiè N, Barberà JA, Frost AE, Ghofrani H-A, Hoeper MM, McLaughlin VV, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med*. 2015 Aug 27;373(9):834–44.
64. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani H-A, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013 Aug 29;369(9):809–18.
65. Lajoie AC, Lauzière G, Lega J-C, Lacasse Y, Martin S, Simard S, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. *Lancet Respir Med*. 2016;4(4):291–305.
66. Sitbon O, Jaïs X, Savale L, Cottin V, Bergot E, Macari EA, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J*. 2014 Jun;43(6):1691–7.
67. van de Veerdonk MC, Kind T, Marcus JT, Mauritz G-J, Heymans MW, Bogaard H-J, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol*. 2011 Dec 6;58(24):2511–9.

68. Madani MM, Auger WR, Pretorius V, Sakakibara N, Kerr KM, Kim NH, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Ann Thorac Surg*. 2012 Jul;94(1):97–103; discussion 103.
69. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, et al. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. *Circulation*. 2016 May 3;133(18):1761–71.
70. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2004 Jun 16;43(12 Suppl S):5S-12S.
71. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med*. 1997 Jan 9;336(2):111–7.
72. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991 Sep 1;115(5):343–9.
73. Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*. 2019 Jan;53(1).
74. Boucly A, Weatherald J, Savale L, Jaïs X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*. 2017;50(2).
75. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J*. 2017;50(2).
76. Kylhammar D, Kjellström B, Hjalmarsson C, Jansson K, Nisell M, Söderberg S, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2017 Jun 1;39(47):4175–81.
77. Humbert M, Farber HW, Ghofrani H-A, Benza RL, Busse D, Meier C, et al. Risk assessment in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019 Jun;53(6):1802004.
78. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. *Am J Cardiol*. 2009 Sep 15;104(6):868–72.
79. Krasuski RA, Hart SA, Smith B, Wang A, Harrison JK, Bashore TM. Association of anemia and long-term survival in patients with pulmonary hypertension. *Int J Cardiol*. 2011 Aug 4;150(3):291–5.
80. Ruitter G, Lankhorst S, Boonstra A, Postmus PE, Zweegman S, Westerhof N, et al. Iron deficiency is common in idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2011 Jun;37(6):1386–91.
81. van Empel VPM, Lee J, Williams TJ, Kaye DM. Iron deficiency in patients with idiopathic pulmonary arterial hypertension. *Heart Lung Circ*. 2014 Mar;23(3):287–92.
82. Jenkins D. Pulmonary endarterectomy: the potentially curative treatment for patients with chronic thromboembolic pulmonary hypertension. *Eur Respir Rev Off J Eur Respir Soc*. 2015 Jun;24(136):263–71.
83. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest*. 1982 Feb;81(2):151–8.
84. Delcroix M, Staehler G, Gall H, Grünig E, Held M, Halank M, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. *Eur Respir J*. 2018;52(5).
85. Taniguchi Y, Jaïs X, Jevnikar M, Boucly A, Weatherald J, Brenot P, et al. Predictors of survival in patients with not-operated chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant*. 2019 Aug;38(8):833–42.

86. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998 Dec 15;98(24):2709–15.
87. Kojda G, Cheng YC, Burchfield J, Harrison DG. Dysfunctional regulation of endothelial nitric oxide synthase (eNOS) expression in response to exercise in mice lacking one eNOS gene. *Circulation*. 2001 Jun 12;103(23):2839–44.
88. Weissmann N, Peters DM, Klöpping C, Krüger K, Pilat C, Katta S, et al. Structural and functional prevention of hypoxia-induced pulmonary hypertension by individualized exercise training in mice. *Am J Physiol Lung Cell Mol Physiol*. 2014 Jun 1;306(11):L986-995.
89. Colombo R, Siqueira R, Becker CU, Fernandes TG, Pires KM, Valença SS, et al. Effects of exercise on monocrotaline-induced changes in right heart function and pulmonary artery remodeling in rats. *Can J Physiol Pharmacol*. 2013 Jan;91(1):38–44.
90. Favret F, Henderson KK, Allen J, Richalet J-P, Gonzalez NC. Exercise training improves lung gas exchange and attenuates acute hypoxic pulmonary hypertension but does not prevent pulmonary hypertension of prolonged hypoxia. *J Appl Physiol Bethesda Md* 1985. 2006 Jan;100(1):20–5.
91. Huber L, Bye H, Brock M. The pathogenesis of pulmonary hypertension – an update. *Swiss Med Wkly* [Internet]. 2015 Oct 19 [cited 2019 Aug 7]; Available from: <http://doi.emh.ch/smw.2015.14202>
92. Gielen S, Adams V, Möbius-Winkler S, Linke A, Erbs S, Yu J, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol*. 2003 Sep 3;42(5):861–8.
93. Harbaum L, Renk E, Yousef S, Glatzel A, Lüneburg N, Hennigs JK, et al. Acute effects of exercise on the inflammatory state in patients with idiopathic pulmonary arterial hypertension. *BMC Pulm Med*. 2016 11;16(1):145.
94. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, et al. Effects of a Rehabilitation Program on Skeletal Muscle Function in Idiopathic Pulmonary Arterial Hypertension: *J Cardiopulm Rehabil Prev*. 2010;30(5):319–23.
95. Keusch S, Turk A, Saxer S, Ehlken N, Grunig E, Ulrich S, et al. Rehabilitation in patients with pulmonary arterial hypertension. *Swiss Med Wkly*. 2017;147:w14462.
96. Hansmann G, Wagner RA, Schellong S, Perez VA de J, Urashima T, Wang L, et al. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. *Circulation*. 2007 Mar 13;115(10):1275–84.
97. Colombo R, Siqueira R, Conzatti A, de Lima Seolin BG, Fernandes TRG, Godoy AEG, et al. Exercise training contributes to H2O2/VEGF signaling in the lung of rats with monocrotaline-induced pulmonary hypertension. *Vascul Pharmacol*. 2016;87:49–59.
98. Marra AM, Egenlauf B, Bossone E, Eichstaedt C, Grünig E, Ehlken N. Principles of Rehabilitation and Reactivation: Pulmonary Hypertension. *Respiration*. 2015;89(4):265–73.
99. Pandey A, Garg S, Khunger M, Garg S, Kumbhani DJ, Chin KM, et al. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. *Circ Heart Fail*. 2015 Nov;8(6):1032–43.
100. Ehlken N, Lichtblau M, Klose H, Weidenhammer J, Fischer C, Nechwatal R, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur Heart J*. 2016 Jan 1;37(1):35–44.
101. Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Airways Group, editor. Cochrane Database Syst Rev* [Internet]. 2017 Jan 18 [cited 2019 Aug 7]; Available from: <http://doi.wiley.com/10.1002/14651858.CD011285.pub2>

102. Ehlken N, Verduyn C, Tiede H, Staehler G, Karger G, Nechwatal R, et al. Economic Evaluation of Exercise Training in Patients with Pulmonary Hypertension. *Lung*. 2014 Jun;192(3):359–66.
103. La Gerche A, Claessen G. Is exercise good for the right ventricle? Concepts for health and disease. *Can J Cardiol*. 2015 Apr;31(4):502–8.
104. Mar PL, Nwazue V, Black BK, Biaggioni I, Diedrich A, Paranjape SY, et al. Valsalva Maneuver in Pulmonary Arterial Hypertension: Susceptibility to Syncope and Autonomic Dysfunction. *Chest*. 2016;149(5):1252–60.
105. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018 Jan;10(1):508–21.
106. Cenedese E, Speich R, Dorschner L, Ulrich S, Maggiorini M, Jenni R, et al. Measurement of quality of life in pulmonary hypertension and its significance. *Eur Respir J*. 2006 Oct;28(4):808–15.
107. Grünig E, Maier F, Ehlken N, Fischer C, Lichtblau M, Blank N, et al. Exercise training in pulmonary arterial hypertension associated with connective tissue diseases. *Arthritis Res Ther*. 2012 Jun 18;14(3):R148.
108. Nagel C, Prange F, Guth S, Herb J, Ehlken N, Fischer C, et al. Exercise training improves exercise capacity and quality of life in patients with inoperable or residual chronic thromboembolic pulmonary hypertension. *PloS One*. 2012;7(7):e41603.
109. Chan L, Chin LMK, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, et al. Benefits of Intensive Treadmill Exercise Training on Cardiorespiratory Function and Quality of Life in Patients With Pulmonary Hypertension. *Chest*. 2013 Feb;143(2):333–43.
110. Bussotti M, Gremigni P, Pedretti RFE, Kransinska P, Di Marco S, Corbo P, et al. Effects of an Outpatient Service Rehabilitation Programme in Patients Affected by Pulmonary Arterial Hypertension: An Observational Study. *Cardiovasc Hematol Disord Drug Targets*. 2017;17(1):3–10.

PART II:

**REHABILITATION IN PATIENTS WITH PULMONARY
ARTERIAL HYPERTENSION AND CHRONIC
THROMBOEMBOLIC PULMONARY HYPERTENSION :
RESULTS FROM THE GRENOBLE EXPERIENCE**

Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are subtypes of pre-capillary pulmonary hypertension (PH). In these conditions, remodeling of the pulmonary vascular bed with an obliterative vasculopathy is responsible for the rise in pulmonary arterial pressure and pulmonary vascular resistance (PVR), and without treatment ultimately leads to right ventricular failure and death. Despite advances in drug therapy with improvements in the short-term survival of patients with PAH, the condition remains incurable. But the recent development of effective medical therapies and the use of combination therapy have considerably improved the prognosis of patients, but also functional capacity and haemodynamics. By contrast, CTEPH is potentially curable by surgery (pulmonary endarterectomy), or interventional balloon pulmonary angioplasty when indicated.

For decades, exercise training has not been recommended for patients with pulmonary arterial hypertension (PAH) due to the fear of a possible risk of sudden cardiac death, arising from worsening hemodynamics and deterioration in right heart function during exercise. It was commonly believed that physical training may contribute negatively to the evolution and progression of PH (1). Because of a lack of efficacy data, supervised exercise rehabilitation was first recommended from 2009 ESC/ERS pulmonary hypertension Guidelines but only in deconditioned PAH patients in a highly supervised setting with avoidance of excessive physical activity (exercise training (ET) remained in class IIa recommendation with a level of evidence B) (2). And yet, reduced exercise capacity in PH is common and associated with anxiety disorders, depression, skeletal muscle dysfunction and compromised quality of life (3,4).

Since then, more studies in rather small cohorts of patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) have shown beneficial effects of ET as add-on to medical therapy by improving symptoms, exercise capacity and quality of life, with reassuring data on safety (5–8). However, it must be emphasised that the patients in these studies were all in a stable condition on optimised PAH-targeted drug therapy (such as endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin analogues, calcium-channel blockers, and guanylate cyclase stimulators) for at least 2 or 3 months, under close supervision in highly specialised PAH expert centres, and the training was specially designed for PAH patients.

In the updated guidelines of 2015 (9), supervised PAH rehabilitation is recommended for stable patients with the best standard of pharmacological treatment and in stable clinical condition and should be implemented by centres experienced in both PAH patient care and rehabilitation of patients (class IIa recommendation, evidence level B). However, there is no published guidelines available detailing how exercise rehabilitation should be carried out. Therefore, this recommendation is limited by the gaps in the knowledge about the optimal method of rehabilitation, programme duration, and intensity of the exercise training.

Patients are often unaware of their own physical limits and, especially for PH patients, it is essential to supervise exercise training when needed during the follow-up and to avoid over-exercise to prevent adverse effects of exercise. Also, rehabilitation not only consists of exercise training, but also includes a multidisciplinary team (including cardiology and respiratory medicine physicians, specialised nurses, radiologists, access to psychological and social work support), which provides informations, counselling and therapeutic interventions.

To facilitate treatment decision for patients with PAH, the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) for the diagnosis and treatment of pulmonary hypertension (9) and the 2018 Proceedings of the 6th World Symposium on Pulmonary Hypertension (10) proposed a dynamic risk stratification strategy, and recommend regular risk assessment at expert PH centres using clinical, echocardiographic, exercise, biochemical, and hemodynamic parameters. However, the effect of exercise training on risk assessment is has not yet been fully established.

We apply the risk assessment criteria from the 2015 ESC/ERS guidelines to a retrospective cohort of patients with PAH or CTEPH who practice rehabilitation with exercise training programme.

The study aimed to evaluate the feasibility of the rehabilitation of patients with PAH or CTEPH, in real life like practiced in a French centre, and to assess the evolution of the risk stratification of these patients. Finally, we evaluate the safety and beneficial effects of cardiac rehabilitation and exercise training in patients; and if data are encouraging, we want to promote the development of PH reeducation in France and identify which patients would benefit from rehabilitation.

Methods

Patients selection

This monocentric study was a retrospective analysis of data from consecutive PAH patients and CTEPH patients admitted in our cardiac rehabilitation centre. All patients were previously hospitalised in PH expert centre, with whom we work closely. Right heart catheterization was performed in all patients, then the expert centre ascertained the PAH or CTEPH diagnosis, decided on the therapy project, started the drug titration if required, and could refer patients to our rehabilitation centre if clinically stable, even if the treatment titration was still in progress. Patients meeting inclusion criteria were enrolled between March, 2010 and May, 2019. The observational period ended in September, 2019. Follow-up time was calculated from the date of the rehabilitation.

Study population

Eligible patients included adults aged over 18 years with confirmed diagnosed PAH of any aetiology and CTEPH by the expert PH centre, then admitted for a cardiac rehabilitation. Patients were not supposed to be stable and compensated under optimized medical therapy before entering the study. But for safety reasons, the clinical and functional status were assessed by PH expert centre, before referring the patient either in rehabilitation day hospital or in a classical rehabilitation hospitalisation stay.

In addition to PH-specific drug therapy if needed, patients also received standard supportive therapy that include oral anticoagulants, diuretics, oxygen, and iron substitution.

Outcome measures

Before the rehabilitation and during the follow-up, most of patients have regular evaluation in the expert PH centre and the rehabilitation centre. Functional status and clinical signs of right heart failure was assessed. Thereby, a 6-minutes walking test was carried out before exercise training programme and at the end, when clinically possible. In the same way as biology. Also, an echocardiography was performed before entering the rehabilitation and right after (if the echocardiography was not available at the end of exercise training programme, the first echocardiography during the follow-up was considered). Systolic pulmonary artery pressures

(PASP) were estimated from tricuspid regurgitation velocity. Furthermore, the right heart catheterization (RHC) before and after rehabilitation, when available, were analyzed.

Rehabilitation programme

Patients were supervised either in a day hospital, or in a classical hospitalisation stay, by an expert care team composed of cardiologist physicians, nurses, pharmacists, dietician, physiotherapists, psychologist, social worker.

It is important to consider potential limiting factors (orthopedic or rheumatologic limitation, sequelae of stroke...) requiring a programme adaptation. Exercise testing are performed (cardiac stress test, cardiopulmonary exercise testing, or 6-minute walk) to establish the training programme at the beginning.

During rehabilitation, PH-specific drug therapy could not be introduced, but doses could be adapted.

The exercise training programme consists of :

- Endurance training:
 - o low-intensity bicycle ergometer training (e.g 5 to 50 watts) in a supervised and monitored setting; up to 30 minutes once or twice a day, 5 days a week. The training intensity was increased with respect of the individual tolerability and improvement. The first session lasted 10 to 25 minutes, with an initial intensity which corresponds to 50% of the maximum load reached in the initial effort test, with or without interval training (a lower workload for 30 seconds and a higher workload for 1 minute (eg, 20 to 35 W)). The sessions' length was increased progressively to 30 minutes. The workload was also raised progressively (+5W), according to patient's exercise tolerance and pulse rate (target heart rate corresponding to 60% to 80% of the maximum heart rate).
 - o treadmill walking, if the patient was not able to practice bicycle ergometer training (most often for rheumatological problems). The first session lasted 10 to 20 minutes with a speed of 2 km/h with 0% incline, then duration, speed and incline were increased progressively.
- Respiratory therapy, including breathing techniques, Yoga, and strengthening of respiratory muscles; during 30 minutes twice a day 5 days a week,

- Some patients practice dumbbell training of single muscle groups (8 to 10 moves, 10 times with low weights: 500gr to 1 kg) in order to improve muscle mass and stamina.
- Outside supervised walk, 30 minutes daily, 5 days a week.

Heart rate, oxygen saturation and rating of perceived exertion were monitored during bicycle ergometer training or treadmill. Patients with or without oxygen therapy at baseline who had oxygen desaturation less than 90% during exercise, received a higher oxygen flow or had oxygen therapy introduction. When patients' heart rate reaches more than 120 beats per minute, or oxygen saturation fell to <85%, training was reduced. The perceived exertion should not exceed 4 from the Borg rating of perceived exertion CR10 scale (somewhat hard exertion), otherwise training was reduced or stopped. The subjective evaluation and experience of the care team also matters. As a consequence, physicians and physiotherapists could adapt the programme to each individual case.

It is important for PH patient to avoid hard exertion, and carrying of heavy loads. The team must be very careful about history of syncope or other cardiac symptoms (palpitations, chest pain, dizziness, lightheadedness...). If it is, a watchful supervision is needed.

Risk assessment and outcomes

To facilitate treatment decision for patients with PAH, the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) for the diagnosis and treatment of pulmonary hypertension (9) proposed a dynamic risk stratification strategy (cf annex 1) and recommend regular risk assessment at expert PH centres using clinical, echocardiographic, exercise, biochemical, and hemodynamic parameters.

These risk stratification groups are applicable at the time of diagnosis, and during follow-up for prognostication. Patients can be categorized as low-, intermediate-, or high-risk, with an estimated 1-year mortality of <5%, 5–10%, and >10%, respectively. The goal of PAH treatment is achieving and maintaining a low-risk profile. Studies showed that this risk assessment accurately predicted the risk of death or lung transplantation in newly diagnosis-PAH patients at the time of diagnosis and during the follow-up. The number of low-risk criteria achieved during the first year of follow-up is also associated with better prognosis than the number of low-risk criteria present at baseline (11). Some studies suggest that the ESC/ERS risk assessment may be applicable in patients with medically treated CTEPH (12,13).

However, most of the variables used in risk assessment are based on expert opinion with low levels of evidence, therefore more studies are needed to check the accuracy of this risk assessment during the follow-up. Moreover, the effect of exercise training on risk assessment is has not yet been fully established.

Following a strategy proposed by KYLHAMMAR et al., an abbreviated version of the 2015 ESC/ERS pulmonary risk stratification strategy was performed : we collect 8 variables recommended for PAH risk stratification in the 2015 ESC/ERS treatment guidelines (WHO functional class, 6MWD, NT-pro BNP, right atrial (RA) area, pericardial effusion, cardiac index, RAP, SvO₂) (14). The cut-off values proposed in the guidelines were graded from 1 to 3 (1: low risk, 2: intermediate risk and 3: high risk). If a 6-min walking test (6MWT) was registered as non-achievable due to clinical condition, it was assigned a grade of 3. The sum of all grades was divided by the number of available variables, which gave a mean grade for each patient. Then it was rounded to the nearest integer, which was used to define the patient's risk group from 1 to 3 where 1= 'Low risk', 2= 'Intermediate risk', and 3= 'High risk'. Risk stratification were made from baseline assessments and from follow-up assessments, which allows to analyze the evolution of the risk assessment.

Adverse events were recorded during the study period. Transplant-free survival time was calculated from the beginning of rehabilitation to the date of last follow-up, death or lung transplantation, for survival analyses. In patients who died, we provided the most likely cause of death, without independent adjudication.

Statistics

Statistical analyses were performed using Excel and Medistica.pvalue.io. The difference of the mean grade at baseline and at follow-up was calculated. Survival was analyzed using Kaplan–Meier method and log-rank test. Survival was compared between the different risk groups as assessed at follow-up. $P < 0.05$ was considered statistically significant. Continuous data are presented as mean +/- standard deviation.

Results

Between 2010 and 2019, 41 patients were included (mean age 59,6 +/- 18,1 years-old). The majority of patients were female (60,9 %), with PAH (n= 23 (56,1%)). Patients with CTEPH were 43,9% (n=18). Most patients had no clinical signs of right heart failure (83%) and were in

WHO/NYHA functional class III (45 %) at baseline, whereas 40 % were in functional class II, and 15 % were in functional class IV. Initial treatment consisted of dual therapy in 43,9 % of the patients, monotherapy in 17%, triple therapy in 19,5%, and finally 19,5% had no specific therapy. A majority of patients also received supportive therapy consisting of oral anticoagulants (78,0%), diuretics (65,9%) and oxygen (31,7%). Baseline characteristics are shown in table 1. For the risk analysis, 7 (interquartile range 7-8) variables per patient were assessed at baseline, and 5 (IQR 4- 6) variables were assessed at follow-up.

TABLE 1 Demographics and baseline characteristics of the 41 patients	
	Study population
Subjects, n	41
Age, years	59,6 (+/-18,1)
Female gender, %	60,9
Clinical signs of right heart failure, %	17
WHO FC I/II/III/IV, n	0/16/18/6 (unknown = 1)
6MWD, m (when done)	391,1 (+/- 161) (NP=6)
NT-pro-BNP, ng/L	1973,6 (+/-2690)
Echocardiography	
RA area, cm²	22,7
Pericardial effusion, %	2,5
Heamodynamics	
RAP, mmHg	9,44
mPAP, mmHg	45,2
Cardiac index, L/min/m²	2,37
SvO₂, %	61,4
Supportive therapy	
Anticoagulants, %	78,0
Diuretics, n (%)	27 (65,9)
Supplemental oxygen, %	31,7
Therapy	
No specific therapy, %	19,5
Monotherapy, %	17,1
Dual therapy, %	43,9
Triple therapy, %	19,5
Stability on optimised medical therapy	
< 3 months, %	73,2
> 3 months, %	26,8

TABLE 2 Detailed demographics and baseline characteristics of the patients according to their PH group

	PAH	CTEPH
Subjects, n	23	18
Age, years	50,9 (+/-16,5)	70,8 (+/-13,0)
Female gender, %	56,5	66,7
Clinical signs of right heart failure, %	17,4 (n=4)	16,7 (n=3)
WHO FC I/II/III/IV, n	0/11/9/3	0/5/9/3 (unknown =1)
6MWD, m (when done)	407 (+/-191) (NP= 2)	367 (+/-105) (NP = 4)
NT-pro-BNP, ng/L	1753 (+/-2776)	2298 (+/-2658)
Echocardiography		
RA area, cm²	21,4	25,3
Pericardial effusion, %	4,5	0
Heamodynamics		
RAP, mmHg	9,3	9,6
mPAP, mmHg	49,6	39,9
Cardiac index, L/min/m²	2,47	2,26
SvO₂, %	63,1	58,4
Supportive therapy		
Anticoagulants, %	60	100
Diuretics, %	69,6	61,1
Supplemental oxygen, %	17	50
Therapy		
No specific therapy, %	0	44
Monotherapy, %	17	17
Dual therapy, %	48	39
Triple therapy, %	35	0
Group 4 intervention		
PEA, n	/	6
BPA, n	/	7
PEA and BPA, n	/	1
No intervention, n	/	4
Stability on optimised medical therapy		
< 3 months, % (mean, days)	65 (18,4)	83 (23,4)
> 3 months, % (mean, days)	35 (292,5)	17 (290)

- The mean length of stay (except the weekend day when there was not reeducation session) was 20,3 days (+/- 9,2), which corresponds to almost 4 weeks.

- Endurance training consists of low-intensity bicycle ergometer training and/or treadmill walking. 19 patients had bicycle ergometer training and treadmill walking. 13 patients had only bicycle ergometer training. 2 patients had only treadmill walking. The training intensity was increased with respect of the individual tolerability and improvement.
 - The bicycle ergometer workload reached at the end of rehabilitation was between 10 and 110 W (average workload: 45,8 W), depending on individual cases, with 30 to 60-minute sessions. The mean numbers of sessions per patient was 16,8. Only 1 patient had interval training.
 - Concerning the treadmill programme, the speed ranged between 0,8 to 5,5 km/h (average speed: 3,3 km/h) with 0% to 14% incline (average incline when applicable: 6,4%). The mean numbers of sessions per patient was 12,2.

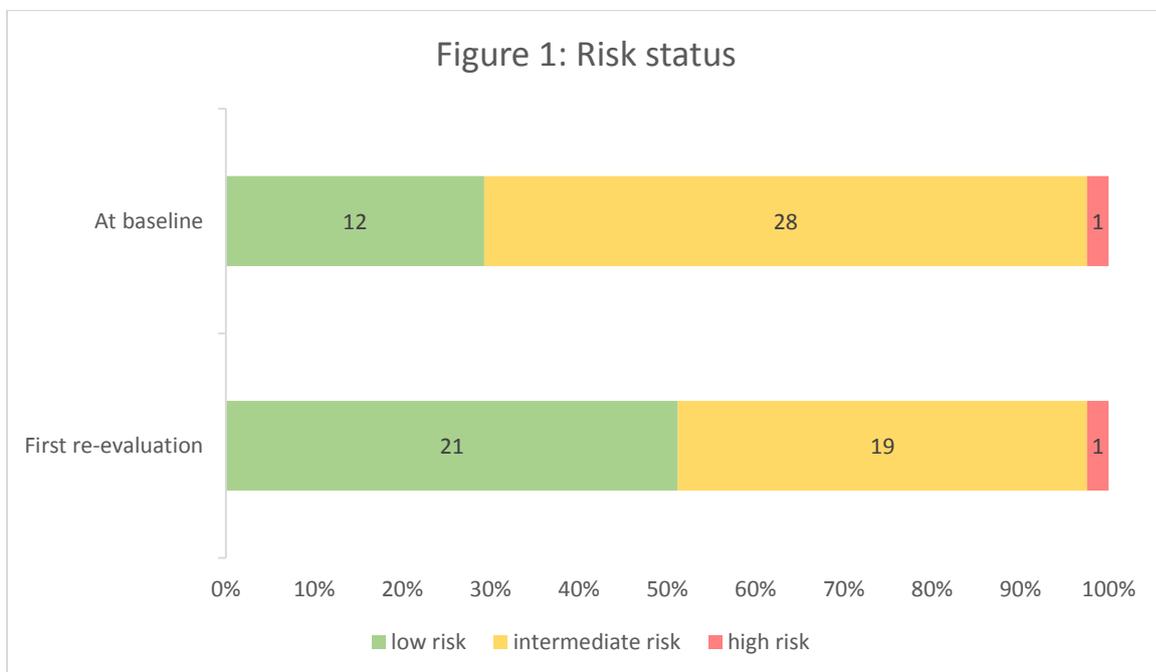
- Patients pursued respiratory group therapy (during 30 minutes twice a day 5 days a week), and most of them went for the outside supervised walk (30 minutes daily 5 days a week, weather permitting). 15 patients practiced dumbbell training of single muscle groups with low weights. The weights ranged between 0,5 to 5,5 kg for upper limb (if we do not consider the higher value, the mean weight was 1,25 kg), and between 0,5 to 13 kg for lower limb (if we do not consider the higher value, the mean weight was 1,45 kg). The mean numbers of sessions per patient was 8,9.

- Among patients in rehabilitation, 6 patients were not in condition to perform endurance exercise training because of a severe exercise intolerance:
 - 1 patient presented tachycardia by atrial fibrillation with clinical signs of global heart failure (55-year-old PAH patient).
 - 2 patients presented recent signs of severe left heart failure, which required oxygen therapy (61-year-old PAH patient and 77-year-old CTEPH patient).
 - 2 patients did not totally recovery from recent interventions with complications (15 days after pulmonary endarterectomy with postoperative pneumopathy, and 5 days after balloon pulmonary angioplasty lung with reperfusion edema with clinical signs of heart failure which required oxygen therapy) (71-year-old CTEPH patient, and 83-year-old CTEPH patient).

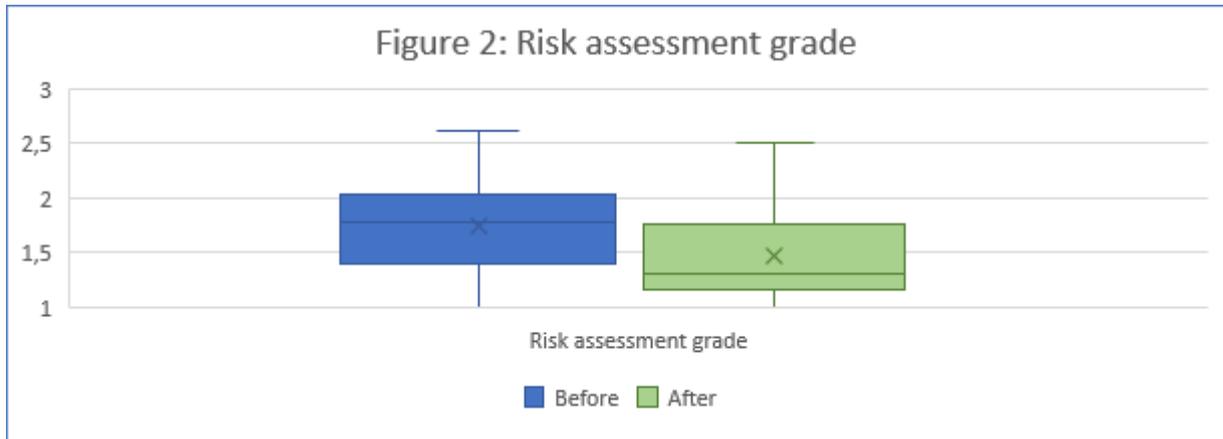
- 1 patient suffered from worsening of the general state as the disease progresses over 8 years, despite multiple treatment attempts (therapeutic failure in a 85-year-old patient).

In these 6 patients, 4 pursued respiratory group therapy; among them 1 practiced dumbbell training, and 2 were able to have an individual supervised walk.

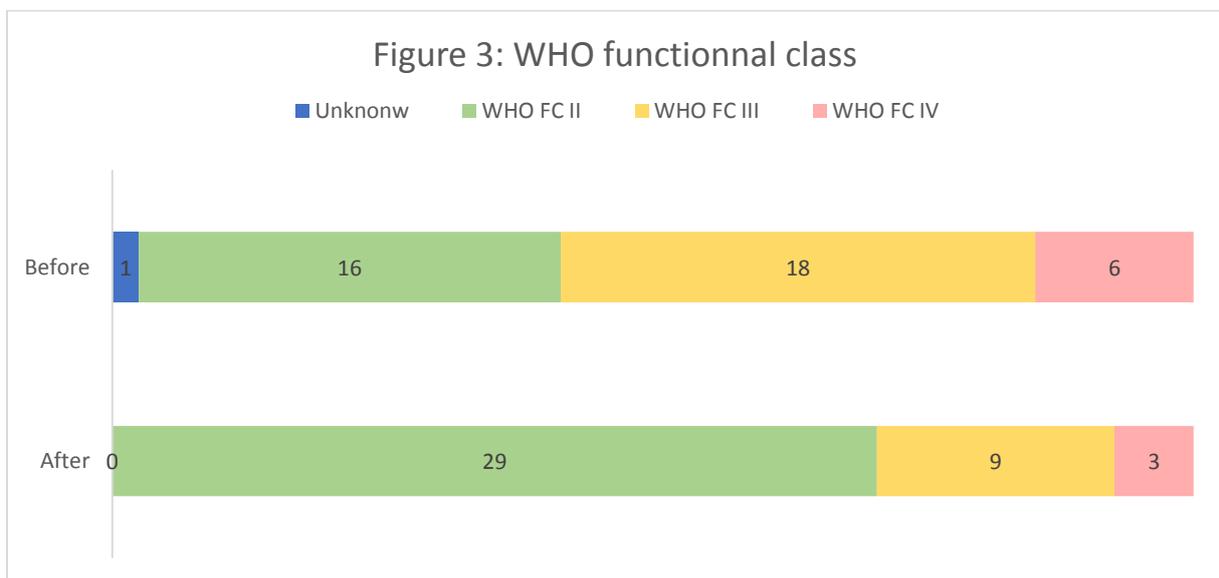
- No patients had PH-specific therapy introduction during the rehabilitation, but 12 patients had specific-drug titration and among them 2 had balloon pulmonary angioplasty. 8 PAH-patients was under continuous intravenous prostacyclin during their stays. Diuretics was also adjusted: during the rehabilitation, diuretics were stopped for 4 patients, the dose were decreased for 9 patients, and increased for 4 patients, finally 2 patients had introduction of diuretics. So, the mean dose of furosemide was lowered from 96,02 to 89,3 mg per day.
- At baseline, 29,3% of patients were in the “low risk”, 68,3% in the “intermediate risk”, and 2,4% in the “high risk” group. After rehabilitation, 51,2% of patients were in the “low risk”, 46,3% in the “intermediate risk”, and 2,4% in the “high risk” group.



- The mean risk assessment grade at baseline was 1,76 (grade scale from 1 to 3). At follow-up, it was 1,51. Which means that the risk assessment grade evolves favorably after rehabilitation, with a statistically significant difference of -0,25 points (95% CI, -0,45 to -0,07).



- The WHO functional class was improved by the rehabilitation: with rehabilitation the number of patients with WHO functional class II increased from 16 to 29. In the same time, the numbers of patients with WHO functional class III or IV decreased respectively from 18 to 9, and from 6 to 3. One patient's status at start rehabilitation was unknown. The mean WHO functional class at baseline was 2,75, and it was significantly improved at the end of the rehabilitation to 2,36 (-0,39, 95% CI, - 0,68 to -0,10).



- As well, 6MWD, when done, increased from 391,1 (+/- 159) m to 444,2 (+/-142) m. The mean difference between groups was 53,1 m (95% CI, -17,7 to +123,9), but did not show a significantly higher increase. The results seem to be better in PAH patients (+ 77 m; 95% CI, - 48 to +202), in comparison with CTEPH patients (+ 24 m; 95% CI, - 82 to +130).
- Mean pulmonary artery pressure improved from 45,2 (+/- 12,4) mmHg at baseline to 38,9 (+/- 10,3) mmHg after rehabilitation. The improvement of the mPAP is statistically significant: - 6,3 mmHg (95% CI, -12,3 to -0,3). NT-proBNP decreased by 463,3 ng/L (from 1973,6 ng/L to 1510,3 ng/L) without being significant (95% CI, - 1754 to + 827). In the same time, there were no renal or hepatic impairment: serum creatinine fell by 5,0 mmol/L (95% CI, - 16,7 to +6,7), and bilirubin was stable 9,5 µmol/L (NS).
- Even for the 6 patients who did not benefit from endurance training, the mean risk assessment grade improved from 2,29 at baseline to 2,10 at follow-up. However, this difference of -0,19 points is not statistically significant (95% CI, -0,63 to 0,25).
- Adverse events occurred in 21,9 % of the patients: sepsis that had to be treated with antibiotics (n=3) (including 2 acute respiratory infections), digestive disorders (n=2) due to adverse effects of PAH specific therapy titration, desaturation during exercise training (n=2). Other events were minor as palpitations (n=1), dizziness (n=1). Among these adverse events, the majority was not linked with physical activity.

TABLE 3 Detailed demographics and baseline characteristics of the patients according to the type of hospitalisation

	Day hospital patients	Conventional hospital patients
Subjects, n	14	27
PH group, n	Group 1 : 11/ group 4 : 3	Group 1 : 12/ group 4 : 15
Age, years	48,0 (+/-18,3)	65,7 (+/-15,1)
Female gender, n (%)	9 (64,3)	16 (59,3)
Clinical signs of right heart failure, n (%)	0 (0)	7 (25,9)
WHO FC I/II/III/IV, n	0/8/5/0 (unknown =1)	0/8/13/6
6MWD, m (when done)	437 (+/-187)	364 (+/-105)
Biology		
NT-pro-BNP, ng/L	1723	2094
Hemoglobin, g/dL	13,9	13,1
Créatinine, µmol/L	82	96
Bilirubin	7	11
CRP, mg/L	10	23
Heamodynamics		
RAP, mmHg	9,7	9,3
mPAP, mmHg	48,0	43,7
Cardiac index, L/min/m²	2,5	2,3
SvO₂, %	66,1	57,9
Supportive therapy		
Diuretics, %	42,9	77,8
Furosemide, mg	52,9	75,7
Supplemental oxygen, %	7,1	44,4
Number of specific-therapy for PH patients	2,0	2,3
Stability on optimised medical therapy		
< 1 months, n (%)	4 (28,6)	12 (66,7)
< 3 months, n (%)	8 (57,1)	15 (81,5)
Time from diagnosis, months	31,5	35,9

TABLE 4 Baseline and final characteristics of the 41 patients		
	Study population at start of rehabilitation	Study population at end of rehabilitation
Clinical signs of right heart failure, n (%)	7 (17)	2 (4,9)
WHO FC I/II/III/IV, n	0/16/18/6 (unknown = 1)	0/29/9/3
Mean WHO FC	2,75 (+/- 0,70)	2,36 (+/- 0,61) *
Mean risk assessment grade	1,76	1,51 *
6MWD, m (when done)	391,1 (+/- 161) (NP=6)	444,2 (+/-143) (NP=4) (NS)
Biology		
NT-pro-BNP, ng/L	1973,6	1510,3 (NS)
Hemoglobin, g/dL	13,3	13,5 (NS)
Créatinine, µmol/L	91,21	86,2 (NS)
Bilirubin	9,54	9,58 (NS)
Echocardiography		
LVEF, %	60,7	61,8 (NS)
TAPSE, mm	17,8	19,0 (NS)
RA area, cm²	22,7	21,1 (NS)
Pericardial effusion, n (%)	1 (2,5)	3 (7,3) (NS)
Heamodynamics		
RAP, mmHg	9,44 (+/- 5,2)	5,9 (+/- 3,2) *
mPAP, mmHg	45.2 (+/- 12,4)	38.9 (+/- 10.3) *
Cardiac index, L/min/m²	2,37 (+/- 0,77)	2,78 (+/- 0,83) (NS)
SvO₂, %	63,2 (+/- 9,2)	66,3 (+/- 9,1) (NS)
Supportive therapy		
Anticoagulants, n (%)	32 (78,0)	32 (78,0)
Diuretics, n (%)	27 (65,9)	25 (61,0)
Supplemental oxygen, n (%)	13 (31,7)	11 (26,8)
Number of specific therapy 0/1/2/3, n	8/7/18/8	8/7/18/8
Therapeutic intervention		
Therapeutic titration during the month prior to rehabilitation, n (%)	21 (51)	/
Drug titration, n (%)	/	12 (29,3)
Ballon pulmonary angioplasty, n (%)	/	2 (4,8)

Discussion

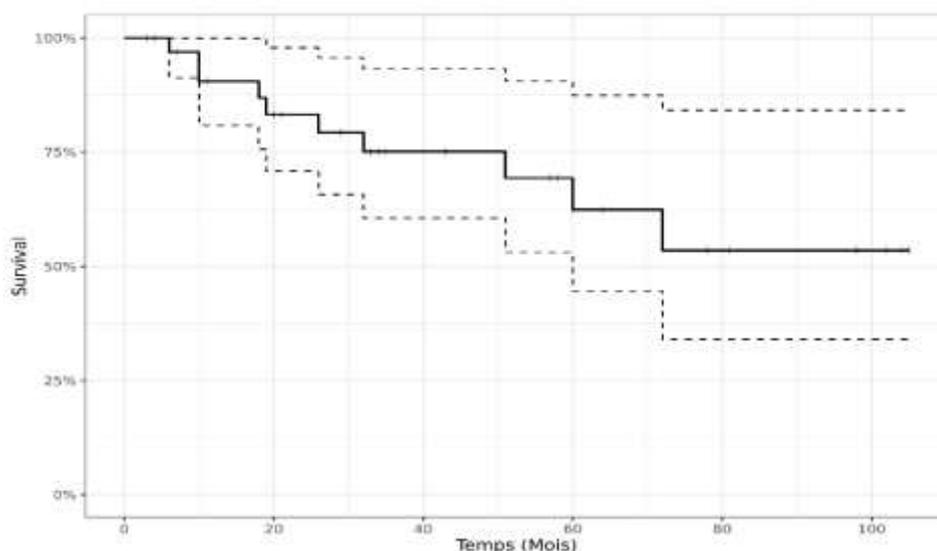
The present study is a retrospective study from consecutive diagnosed PAH patients and CTEPH patients who benefited from cardiac rehabilitation in our rehabilitation centre.

According to the actual PH guidelines, treatment decisions should be based on risk assessments, and the main objective of PH therapy is achieving or maintaining a low-risk profile. This treatment goal was achieved in the majority of our patients: following risk stratification proposed by KYLHAMMAR et al. there was 29% low-risk profile patients at the beginning, and 51% at follow-up. The rehabilitation programme seems to be beneficial, even to frail patients, and also to patients who did not practice endurance training. The effect of exercise and respiratory training was associated with significant improvements in risk assessment grade, WHO/NYHA functional class, and haemodynamic parameters (mPAP and RAP). Only few patients performed cardiopulmonary exercise testing, that is a reason why the evolution of VO₂ and workload at the anaerobic threshold was not analysed. With such a small patient cohort, the mean 6MWD improvement from baseline was 53,1 m and was not significant in our study, but exceeding the minimum clinically important difference of 33 m by far (15). However, the absolute value is comparable to others studies : a meta-analysis, including 16 prospective intervention studies with 469 PH participants, observed up to 53 m improvement in 6MWD at 15 weeks with exercise training on pooled analysis (weighted mean difference, 53,3 m; 95% CI, 39,5–67,2) (16). In comparison, some therapy randomized controlled trials showed significant effects with lower improvements : patients who received initial dual therapy with ambrisentan (10 mg) plus tadalafil (40 mg), in the AMBITION trial, had a 48,98 m median change from baseline after 24 weeks (17). In the SERAPHIN trial, at month 6, the 6-minute walk distance had increased by a mean of 12,5 m in the group that received 10 mg of macitentan (18). In the GRIPHON trial, at week 26, the 6-minute walk had increased by 4,0 m from baseline in the selexipag group (maximum dose, 1600 µg twice daily) (19).

When comparing the type of hospitalisation (day hospitalisation or conventional hospitalisation), it is noted that patients who benefit from rehabilitation during day hospitalisation, are less frail than inpatients at baseline: they are younger, have no sign of right heart failure, have a better 6MWD and functional class (with no WHO FC IV), have less diuretics or oxygen therapy, have better biological and hemodynamic parameters, and are more likely to be in a stable condition on optimised PH targeted medical therapy.

In our study, a total of 21,9% of participants suffered adverse events, the majority of which was not linked with physical activity. No major adverse events such as progression of right heart failure or death, were reported. In one of the largest studies from the highly expert centre of Heidelberg (183 patients), a total of 13,6% of their participants had adverse events (7). A meta-analysis including 16 prospective intervention studies, reported adverse events in 11,3% of participants (6,6% infections, plus 4,7% minor side effects such as dizziness, presyncope, syncope, palpitations, hypotension, or oxygen desaturation) (16). From these experiences, low-dose exercise and respiratory training programme under expert supervision with oxygenotherapy (when needed), is relatively safe, with no major adverse events.

In our study, the expert PH centre defined the treatment then rehabilitation centre could adapt the doses. No patients had specific-therapy introduction during the rehabilitation, but 21 patients had had a therapeutic titration during the month prior to rehabilitation, and 12 patients had specific PH-drug titration during their stay, nevertheless we had no major adverse event. Therefore the selection of PH patients is crucial to guaranty the safety of the rehabilitation, but patients do not have to be in clinically stable condition on optimised PH targeted therapy for at least 2 months (as can be seen from rehabilitation studies). Exercise training is a beneficial therapy with a good safety profile when closely supervised, in participants who were assessed in a PH expert centre before beginning the rehabilitation.



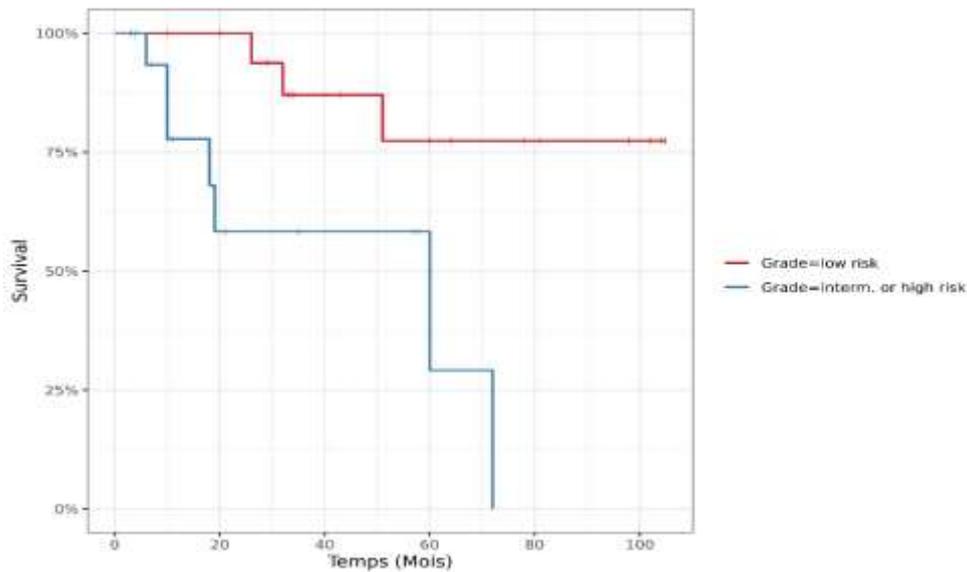


Figure 4: Survival (alive free from heart-lung transplantation)
 (A): survival in the study population
 (B): survival based on follow-up risk group ($p < 0,01$)

After a median observational follow-up of 33 months (IQR 10,5-60,0), 31 (75%) patients had no clinical event, which was defined as first occurrence of any of the following event: death or heart-lung transplantation. 8 patients died, and 2 had a transplantation. Causes of death were right heart failure (n=1), sudden death (n=2), severe hypoxemia (n=2), cancer (n=2) and unknown (n=1). It is interesting to note, patients who remained or reached a “low risk” profile after rehabilitation, have a better prognosis ($p < 0,01$). Therefore, changes in the risk category, seem to be an accurate predictor of long-term survival.

In our study, the survival rate was 80,5%, after a median follow-up of 33,0 months (IQR 10,5-60,0). It is similar to large cohorts of newly diagnosed patients:

- The cohort from Boucly et al. in 2017, 1017 PAH patients were enrolled from the French registry (mean age 57 years, 59% female, 75% idiopathic PAH). After a median follow-up of 34 months, 238 (23%) patients had died (11).
- The cohort from Delcroix et al. in 2017, 561 newly diagnosed inoperable CTEPH patients from COMPERA registry. Overall survival estimates of 75% at 3 years (13)
- A meta-analysis of 16 prospective intervention studies with a median follow-up of 29,5 months (range, 21–36 months), the proportion of participants alive was 91% (12 deaths), and the proportion of participants with transplant-free survival was 89% (16).

Our study has limitations requiring cautious interpretation of our findings. Indeed, the present study was a retrospective trial (without placebo-controlled, nor double-blind design), and limited by the small number of patients, and by the population heterogeneity of group 1 (including those with IPAH, heritable PAH, anorexigen-induced PAH, congenital heart disease, and portopulmonary hypertension) and group 4 PH patients (including postoperative patients (PEA or BPA) and inoperable patients). Patients belonged to group 1 or 4 PH, therefore, the benefits of exercise training observed may not be applicable to patients with other classes of pulmonary hypertension. Due to retrospective trial design, it is subject to missing values, in particular in patients who had no haemodynamic reassessment or were not followed by our PH expert centre. Finally, it may be mentioned that, in the early 2010's, the use of combination therapy in patients with PAH was less developed due to the lack of evidence; this way the prognosis of early enrolled patients may be more pejorative.

Germany have 39 PH expert centres, but only one PH rehabilitation centre in Heidelberg (20). Most published studies were conducted in this highly specialised rehabilitation centre under close expert supervision (5,21). They established a 3-week inpatient training programme followed by a home-based training. During the in-hospital rehabilitation, the physicians stay in daily contact with the PH experts. Patients received optimized PH-targeted medical treatment over at least 2 months before starting the programme in order to provide a good safety profile, and medication remained unchanged during the study period. In comparison, France have fewer PH centre (24 in metropolitan France and 2 in french overseas departments) (cf Annex 2) (22), and throughout the country, practices are disparate in term of rehabilitation programme among patients with PH.

With our study, we wanted to evaluate the feasibility, beneficial effects and safety of the rehabilitation of patients with PAH or CTEPH, with one of the largest cohort in France, and by this way we want to promote the development of PH reeducation in France.

Exercise training should not be initiated in a non-supervised and not adequately monitored setting. From our data, we can formulate and suggest different components of the rehabilitation programme in patients with PAH or CTEPH: the supportive therapy is started when needed, and patients must be referred to specialised PH expert centres to confirm the diagnosis. After that, the expert centre must evaluate clinical status of patients, and also determine the PH-targeted strategy with or without rehabilitation. The treatment must be introduced before entering the rehabilitation programme. Exercise trainings should be implemented by rehabilitation centres experienced in frail patients reeducation (e.g. patients with severe heart failure), and which are working in close collaboration with PH expert care centre. For safety reasons, exercise training could be started in an in-hospital setting, especially if patients are vulnerable (e.g. elderly people, patients with sign of right heart failure, low exercise capacity, WHO FC IV, comorbidities, high dose of diuretics or oxygen therapy). If the safety process is respected, participants no need to be all in a stable condition on optimised PAH-targeted drug therapy. At first, the rehabilitation centre determines initial exercise training intensity, and counsel patients and trainers. The physical approach consists of low-intensity training in a close supervised and monitored setting, low-dose dumbbell training, and respiratory therapy. Patients need to be trained how to perceive their own physical limits and to perform exercise training at home in a safe way.

But despite all of this, a standardised programme not flexible is not realistic, because programme have to be constantly adapted by the care team for each patient. To this end, it is essential to have a daily cooperation between physicians and physical therapists (or other professionals) to ensure safety in rehabilitation.

The reeducation not only consists of exercise and respiratory training; in fact the multidisciplinary approach allows to offer therapeutic education, information, supervised exercise training, psychological, and nutritional support if needed, and social service. PH patients have to face various difficulties and stress factors in everyday life, such as physical disabilities, contraindications to have a pregnancy, high cost of treatment, and unemployment. Many studies highlighted that the rehabilitation program could serve as an adjuvant to manage depression and anxiety in this patients (23)

Conclusion

In our study, the rehabilitation programme improved functional capacity, and hemodynamic parameters in patients with PAH or CTEPH. The 6-minute walk distance improvement exceeded by far the minimal important difference (MID) of 33 m, but was not statistically significant in our study. Also, the results of this study suggest that rehabilitation improves the risk assessment grade, even in frail patients or in patients who are not in stable condition on optimised medical therapy. In addition, it helps patients to remain or reach “low-risk” profile, which is associated with a better survival. Moreover, in a supervised setting, it is safe with no major adverse events.

We are still waiting for specific recommendations about exercise in PH, but in the meantime rehabilitation programmes must be suggested as a secure and effective tool with synergistic effect with specific-PH therapy, to improve exercise capacity in PAH and CTEPH patients.

These data are encouraging and warrant further randomized trials to develop the optimal training component.

ANNEXES

Table 13 Risk assessment in pulmonary arterial hypertension

Determinants of prognosis* (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope ^b	Repeated syncope ^c
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO ₂ >15 ml/min/kg (>65% pred.) VE/VCO ₂ slope <36	Peak VO ₂ 11–15 ml/min/kg (35–65% pred.) VE/VCO ₂ slope 36–44.9	Peak VO ₂ <11 ml/min/kg (<35% pred.) VE/VCO ₂ slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm ² No pericardial effusion	RA area 18–26 cm ² No or minimal pericardial effusion	RA area >26 cm ² Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m ² SvO ₂ >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m ² SvO ₂ 60–65%	RAP >14 mmHg CI <2.0 l/min/m ² SvO ₂ <60%

6MWD = 6-minute walking distance; BNP = brain natriuretic peptide; CI = cardiac index; CMR = cardiac magnetic resonance; NT-proBNP = N-terminal pro-brain natriuretic peptide; pred. = predicted; RA = right atrium; RAP = right atrial pressure; SvO₂ = mixed venous oxygen saturation; VE/VCO₂ = ventilatory equivalents for carbon dioxide; VO₂ = oxygen consumption; WHO = World Health Organization.

*Most of the proposed variables and cut-off values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for IPAH and the cut-off levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

^bOccasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

^cRepeated episodes of syncope, even with little or regular physical activity.

Annex 1 : from Galiè et al. (2)



Annex 2 : from HTaPFrance (22)

THÈSE SOUTENUE PAR : Thomas BARRET

TITRE :

LA READAPTATION CARDIAQUE DANS LA PRISE EN CHARGE DE
L'HYPERTENSION ARTERIELLE PULMONAIRE ET DE L'HYPERTENSION
PULMONAIRE THROMBOEMBOLIQUE CHRONIQUE : RÉSULTATS DE
L'EXPÉRIENCE GRENOBLOISE

CONCLUSION :

L'activité physique a longtemps été déconseillée chez les patients atteints d'une hypertension pulmonaire, par crainte d'une altération de la fonction ventriculaire droite. Malgré des études récentes qui ont montré un effet bénéfique de la réadaptation supervisée en centre expert chez des patients atteints d'hypertension artérielle pulmonaire (HTAP) ou d'hypertension pulmonaire thromboembolique chronique (HTP-TEC), il n'y a pas de consensus sur la pratique de la réadaptation, dont la réalisation reste très disparate selon les centres en France.

Cette étude de vraie vie rétrospective montre un effet bénéfique de la réadaptation cardiaque sur la classe fonctionnelle NYHA (29% des patients sont en classe NYHA III ou IV lors du suivi, contre 59% avant la réadaptation), les paramètres hémodynamiques tels que la PAPm (différence moyenne, -6,3 mmHg, 95% CI, -2,3 to -0,3) et la pression auriculaire droite. Par ailleurs, la distance parcourue au test de marche de 6 minutes progresse au-delà de différence minimale pertinente (33 m), mais n'est pas statistiquement significative (53,1 m, 95% CI, -17,7 to 123,9). On note également une amélioration du score de risque (-0,25, 95% CI, -0,45 to -0,07), même chez les patients les plus fragiles, ou ceux qui ne sont pas sous un traitement stabilisé et optimisé.

Quand la réadaptation est supervisée dans un centre expérimenté, la tolérance est satisfaisante. 21,9% des participants ont souffert d'effets indésirables, dont la majorité n'est pas en lien avec l'exercice physique ; en outre aucun événement majeur n'a été rapporté (progression de l'insuffisance cardiaque droite, ou décès).

En attendant des recommandations précises sur la pratique de l'exercice physique dans l'hypertension pulmonaire, la réadaptation cardiaque doit être proposée en association au traitement spécifique afin d'améliorer les capacités physiques des patients atteints d'HTAP ou de HTP-TEC.

Ces résultats encouragent à diffuser plus largement la réadaptation cardiaque dans cette population en France. Néanmoins, des études prospectives multicentriques sont nécessaires afin d'affiner nos connaissances dans ce domaine.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 6/11/19

LE DOYEN



Pour le Président
Pr. Patrice MORAND
Le Doyen de Médecine
Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



Pr. Bruno DEGANO

BIBLIOGRAPHY

1. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet Lond Engl.* 1998 Aug 29;352(9129):719–25.
2. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009 Oct;30(20):2493–537.
3. Löwe B, Gräfe K, Ufer C, Kroenke K, Grünig E, Herzog W, et al. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med.* 2004 Dec;66(6):831–6.
4. Osadnik CR, Rodrigues FMM, Camillo CA, Loeckx M, Janssens W, Doms C, et al. Principles of Rehabilitation and Reactivation. *Respiration.* 2015;89(1):2–11.
5. Mereles D, Ehlken N, Kreuzer S, Ghofrani S, Hoeper MM, Halank M, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation.* 2006 Oct 3;114(14):1482–9.
6. Grünig E, Ehlken N, Ghofrani A, Staehler G, Meyer FJ, Juenger J, et al. Effect of Exercise and Respiratory Training on Clinical Progression and Survival in Patients with Severe Chronic Pulmonary Hypertension. *Respiration.* 2011;81(5):394–401.
7. Grünig E, Lichtblau M, Ehlken N, Ghofrani HA, Reichenberger F, Staehler G, et al. Safety and efficacy of exercise training in various forms of pulmonary hypertension. *Eur Respir J.* 2012 Jul;40(1):84–92.
8. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJH, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J.* 2009 Sep 1;34(3):669–75.
9. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016 Jan 1;37(1):67–119.
10. Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J.* 2019 Jan;53(1).
11. Boucly A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J.* 2017;50(2).
12. Humbert M, Farber HW, Ghofrani H-A, Benza RL, Busse D, Meier C, et al. Risk assessment in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2019 Jun;53(6):1802004.
13. Delcroix M, Staehler G, Gall H, Grünig E, Held M, Halank M, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. *Eur Respir J.* 2018;52(5).

14. Kylhammar D, Kjellström B, Hjalmarsson C, Jansson K, Nisell M, Söderberg S, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2017 Jun 1;39(47):4175–81.
15. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2012 Sep 1;186(5):428–33.
16. Pandey Ambarish, Garg Sushil, Khunger Monica, Garg Sonia, Kumbhani Dharam J., Chin Kelly M., et al. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension. *Circ Heart Fail*. 2015 Nov 1;8(6):1032–43.
17. Galiè N, Barberà JA, Frost AE, Ghofrani H-A, Hoeper MM, McLaughlin VV, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med*. 2015 Aug 27;373(9):834–44.
18. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani H-A, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013 Aug 29;369(9):809–18.
19. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2015 Dec 24;373(26):2522–33.
20. Pulmonale Hypertonie e.V. – pulmonale hypertonie (ph) e.v. Gemeinnütziger Selbsthilfeverein. Wir sind Betroffene und haben uns mit unseren Freunden zu dem Verein pulmonale hypertonie (ph) e.v. zusammengeschlossen, um den Erkrankten und deren Familien, in ihrem persönlichen Schicksal nach der Diagnose Lungenhochdruck, zu helfen. [Internet]. [cited 2019 Sep 29]. Available from: <https://www.phev.de/professionals.html#phevtabs1>
21. Marra AM, Egenlauf B, Bossone E, Eichstaedt C, Grünig E, Ehlken N. Principles of Rehabilitation and Reactivation: Pulmonary Hypertension. *Respiration*. 2015;89(4):265–73.
22. HTaPFrance - Je m'informe [Internet]. [cited 2019 Sep 29]. Available from: http://www.htapfrance.com/je-m-informe/centre_traitement.asp?rubrique=2&page=1
23. Dalla Vecchia LA, Bussotti M. Exercise training in pulmonary arterial hypertension. *J Thorac Dis*. 2018 Jan;10(1):508–21.

LA READAPTATION CARDIAQUE DANS LA PRISE EN CHARGE DE L'HYPERTENSION
ARTERIELLE PULMONAIRE ET DE L'HYPERTENSION PULMONAIRE
THROMBOEMBOLIQUE CHRONIQUE : RÉSULTATS DE L'EXPÉRIENCE GRENOBLOISE

RESUME

Introduction : Alors que l'activité physique a longtemps été déconseillée chez les patients atteints d'une hypertension pulmonaire, des études récentes ont montré que la réadaptation en centre expert pouvait avoir un rôle bénéfique dans la prise en charge de l'hypertension artérielle pulmonaire (HTAP), et l'hypertension pulmonaire thromboembolique chronique (HTP-TEC).

Méthodes : Tous les patients porteurs d'HTAP ou HTP-TEC, admis en rééducation cardiaque entre mars 2010 et mai 2019, ont été évalués de façon rétrospective sur des paramètres fonctionnels, biologiques, et hémodynamiques. Une version abrégée récemment validée de la stratification du risque a été appliquée.

Résultats : 41 patients ont été inclus (âge moyen, 59,6 +/- 18,1 ans). La réadaptation a permis une amélioration du score de risque (différence moyenne, -0,25, 95% CI, -0,45 to -0,07), de la classe fonctionnelle NYHA et de paramètres hémodynamiques tels que la PAPm (- 6,3 mmHg, 95% CI, -2,3 to -0,3) et la pression auriculaire droite. La distance parcourue au test de marche de 6 minutes progresse au-delà de différence minimale pertinente (33 m), mais n'est pas statistiquement significative (53,1 m, 95% CI, -17,7 to 123,9). 21,9% des participants ont souffert d'effets indésirables non majeurs, dont la majorité n'est pas liée à l'exercice physique.

Conclusion : Chez les patients atteints d'HTAP ou HTP-TEC, la réadaptation pratiquée en milieu supervisé, associée au traitement médical spécifique, permet une amélioration des capacités fonctionnelles, des paramètres hémodynamiques et du pronostic estimé, sans complication majeure.

MOTS-CLES : exercice physique, hypertension pulmonaire, hypertension artérielle pulmonaire, hypertension pulmonaire thromboembolique chronique, réadaptation cardiaque

FILIÈRE : Cardiologie et Maladies Vasculaires

REHABILITATION IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION AND CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION : RESULTS FROM THE GRENOBLE EXPERIENCE

ABSTRACT

Introduction : For decades, patients with pulmonary hypertension (PH) were advised to avoid exercise in fear of deterioration in right heart function. Since then, recent studies have reported that rehabilitation programme in expert centres may have a specific role in the management of pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH).

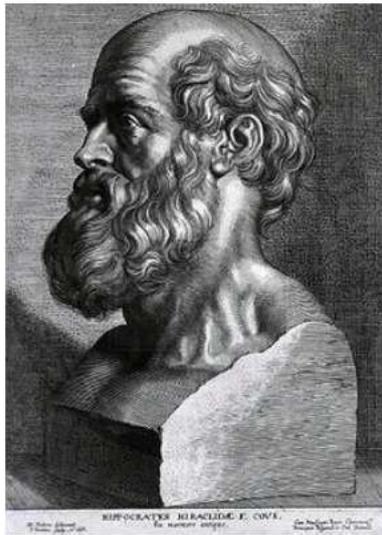
Methods : All consecutive patients with PAH or CTEPH admitted in a French rehabilitation centre between March 2010 and May 2019 were evaluated retrospectively on functional, biological parameters, and haemodynamics. We also apply a recently validated abbreviated versions of the ESC/ERS pulmonary hypertension risk stratification.

Results : 41 patients were included (mean age 59,6 +/- 18,1 years-old). The rehabilitation programme improved the risk assessment grade (-0,25 point, 95% CI, -0,45 to -0,07), the NYHA functional class and haemodynamic parameters including mPAP (- 6,3 mmHg, 95% CI, -12,3 to -0,3) and right atrial pressure. The 6-minute walk distance improvement exceeded by far the minimal important difference of 33 m, but was not statistically significant (53,1 m, 95% CI, -17,7 to 123,9). 21,9% of participants suffered adverse events, the majority of which was not linked with physical activity, and no major adverse events (progression of right heart failure or death) were reported.

Conclusion : Among patients with PAH or CTEPH, the rehabilitation programme, in a supervised setting, as add-on to medical therapy is relatively safe and effective to improve functional capacity, hemodynamic parameters, and risk assessment grade.

KEYWORDS: Physical exercise, Pulmonary hypertension, Pulmonary arterial hypertension, Chronic thromboembolic pulmonary hypertension, Rehabilitation programme

SECTION: Cardiology



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

THÈSE SOUTENUE PAR : Thomas BARRET

TITRE :

LA READAPTATION CARDIAQUE DANS LA PRISE EN CHARGE DE
L'HYPERTENSION ARTERIELLE PULMONAIRE ET DE L'HYPERTENSION
PULMONAIRE THROMBOEMBOLIQUE CHRONIQUE : RÉSULTATS DE
L'EXPÉRIENCE GRENOBLOISE

CONCLUSION :

L'activité physique a longtemps été déconseillée chez les patients atteints d'une hypertension pulmonaire, par crainte d'une altération de la fonction ventriculaire droite. Malgré des études récentes qui ont montré un effet bénéfique de la réadaptation supervisée en centre expert chez des patients atteints d'hypertension artérielle pulmonaire (HTAP) ou d'hypertension pulmonaire thromboembolique chronique (HTP-TEC), il n'y a pas de consensus sur la pratique de la réadaptation, dont la réalisation reste très disparate selon les centres en France.

Cette étude de vraie vie rétrospective montre un effet bénéfique de la réadaptation cardiaque sur la classe fonctionnelle NYHA (29% des patients sont en classe NYHA III ou IV lors du suivi, contre 59% avant la réadaptation), les paramètres hémodynamiques tels que la PAPm (différence moyenne, -6,3 mmHg, 95% CI, -2,3 to -0,3) et la pression auriculaire droite. Par ailleurs, la distance parcourue au test de marche de 6 minutes progresse au-delà de différence minimale pertinente (33 m), mais n'est pas statistiquement significative (53,1 m, 95% CI, -17,7 to 123,9). On note également une amélioration du score de risque (-0,25, 95% CI, -0,45 to -0,07), même chez les patients les plus fragiles, ou ceux qui ne sont pas sous un traitement stabilisé et optimisé.

Quand la réadaptation est supervisée dans un centre expérimenté, la tolérance est satisfaisante. 21,9% des participants ont souffert d'effets indésirables, dont la majorité n'est pas en lien avec l'exercice physique ; en outre aucun événement majeur n'a été rapporté (progression de l'insuffisance cardiaque droite, ou décès).

En attendant des recommandations précises sur la pratique de l'exercice physique dans l'hypertension pulmonaire, la réadaptation cardiaque doit être proposée en association au traitement spécifique afin d'améliorer les capacités physiques des patients atteints d'HTAP ou de HTP-TEC.

Ces résultats encouragent à diffuser plus largement la réadaptation cardiaque dans cette population en France. Néanmoins, des études prospectives multicentriques sont nécessaires afin d'affiner nos connaissances dans ce domaine.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 01/11/19

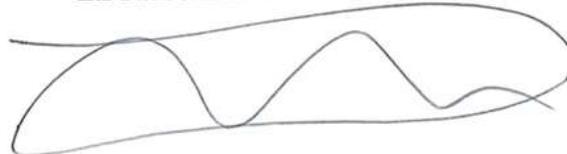
LE DOYEN



Pour le Président
et par délégation
Pr. Patrice MORAND

Le Doyen de Médecine
Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE



Pr. Bruno DEGANO