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ABBREVIATIONS

CHD: congenital heart disease, **COPD:** chronic obstructive pulmonary disease**, Cpc-PH:** combined pre-capillary pulmonary hypertension, **CPFE**: combined pulmonary fibrosis and emphysema, **CR:** cardiac rehabilitation, **CTD-PAH**: connective tissue disease associated with pulmonary arterial hypertension, **CTEPH:** chronic thromboembolic pulmonary hypertension, **DLCO:** diffusion capacity carbon monoxide, **DPG:** diastolic pressure gradient, **DPLD**: diffuse parenchymal lung disease, **EF**: ejection fraction, **FEV1:** forced expiratory volume, **EOB**: exercise oscillatory breathing, **HF**: heart failure, **HFpEF**: heart failure with preserved ejection fraction, **HFrEF**: heart failure with reduced ejection fraction, **ICD**: implantable cardioverter defibrillator, **Ipc-PH:** isolated pre-capillary pulmonary hypertension, **ILD:** interstizial lung disease**, IPAH:** idiopathic pulmonary arterial hypertension**, IPF**: idiopathic pulmonary fibrosis, **LHD**: left heart disease, **LVEF**: left ventricular ejection fraction, **m PAP**: mean pulmonary arterial pressure, **NYHA**: New York Heart Association, **PAH**: pulmonary arterial hypertension, **PAWP:** pulmonary arterial wedge pressure, **PH**: pulmonary hypertension, **PVH**: pulmonary venous hypertension, **PVR**: pulmonary venous resistance, **RV**: right ventricle, **SNPs**: 75 exonic single-nucleotide polymorphisms, **RHC:** right heart catheterization, **TAPSE**: tricuspid annular plane systolic excursion, **UIP:** usual interstizial pneumonia, **6MWD**: six minutes walk distance.

ABSTRACT

Pulmonary hypertension (PH) is a heterogeneous condition defined by elevated mean pulmonary pressure ≥ 20 mmHg measured with right heart catheterization. Left-sided cardiac and lung diseases are the most common causes.

Symptoms in early stages include exertional dyspnea, fatigue and reduced exercise tolerance. With the progression of the disease, symptoms of right ventricular failure such as exertional chest pain, syncope and peripheral congestion may be manifested.

Patients presented with heart failure with reduced or preserved ejection fraction and left- sided valvular diseases are predisposed to manifest pulmonary hypertension.

There are two subgroups in left cardiac disease.

1) It refers to isolated post-capillary pulmonary hypertension which is due to a primary elevation of pressure in the pulmonary arterial system alone.

2) It is called combined post- and pre-capillary pulmonary hypertension with the post-capillary component due to elevation of pressure in the pulmonary venous and pulmonary capillary system (pulmonary venous hypertension). In practice, some patients have mixed pre- and post-capillary features. These patients have poorer prognosis than those of the first subgroup.

Patients with chronic obstructive pulmonary disease in combination with comorbidities and old age have a higher possibility to manifest pulmonary hypertension.

Survival rates seem to be lower in PH due to idiopathic pulmonary fibrosis and combined pulmonary fibrosis with emphysema.

This may be explained by the increased burden of parenchymal lung disease and the pulmonary vascular disease resulting in vascular remodeling.

This review reports pulmonary hypertension as result of left heart and lung diseases.

ΠΕΡΙΛΗΨΗ

Η πνευμονική υπέρταση είναι μια ετερογενής κατάσταση που ορίζεται από αυξημένη μέση πνευμονική πίεση ≥ 20 mmHg στον δεξιό καρδιακό καθετηριασμό. Οι παθήσεις της αριστερής καρδιάς και οι πνευμονικές παθήσεις και είναι το πιο συχνό αίτιο.

Τα συμπτώματα στα πρώιμα στάδια περιλαμβάνουν δύσπνοια προσπάθειας και μειωμένη ικανότητα για άσκηση. Με την πρόοδο της νόσου, μπορούν να εκδηλωθούν συμπτώματα δεξιάς καρδιακής ανεπάρκειας όπως προκάρδιο άλγος στην κόπωση, συγκοπή, και περιφερική συμφόρηση.

Οι ασθενείς που εμφανίζουν καρδιακή ανεπάρκεια με χαμηλό ή διατηρημένο κλάσμα εξώθησης και αυτοί με παθήσεις των αριστερών βαλβίδων της καρδιάς, έχουν μεγαλύτερη πιθανότητα να αναπτύξουν πνευμονική υπέρταση.

Υπάρχουν δύο υποομάδες ασθενών στις παθήσεις της αριστερής καρδιάς.

1) Η πρώτη αναφέρεται στην μεμονωμένη μετα-τριχοειδική πνευμονική υπέρταση που οφείλεται σε πρωτογενείς αυξήσεις των πιέσεων στο πνευμονικό αρτηριακό σύστημα.

2) Η δεύτερη υποομάδα λέγεται συνδυασμένη προ και μετά-τριχοειδική πνευμονική υπέρταση και οφείλεται σε αυξήσεις της πίεσης στο πνευμονικό φλεβικό και τριχοειδικό σύστημα (πνευμονική φλεβική υπέρταση).

Πρακτικά, μερικοί ασθενείς έχουν μεικτά προ και μετά-τριχοειδικά χαρακτηριστικά. Αυτοί οι ασθενείς έχουν χειρότερη πρόγνωση από αυτούς της πρώτης υποομάδας.

Οι ασθενείς με χρόνια αποφρακτική πνευμονοπάθεια σε συνδυασμό με συννοσυρότητες και μεγαλύτερη ηλικία, έχουν μεγαλύτερη πιθανότητα να εμφα-

νίσουν πνευμονική υπέρταση. Τα ποσοστά επιβίωσης φαίνεται να είναι χαμηλότερα σε ασθενείς με ιδιοπαθή πνευμονική ίνωση και σε συνδυασμό πνευμονικής ίνωσης και εμφυσήματος.

Αυτό μπορεί να εξηγηθεί από το αυξημένο φορτίο της νόσου του παρεγχύματος και της πνευμονικής αγγειακής πάθησης όπως προκύπτει από τον αγγειακό ανασχηματισμό.

Η πνευμονική αρτηριακή υπέρταση μπορεί να είναι τυχαίο εύρημα σε ασθενείς με χρόνια αποφρακτική πνευμονοπάθεια ή άλλες πνευμονικές παθήσεις χωρίς να είναι απαραίτητα το αποτέλεσμα της ασθένειας.

Στην εργασία αυτή θα αναφερθούμε στην πνευμονική υπέρταση ως αποτέλεσμα παθήσεων της αριστερής καρδιάς και πνευμονικών παθήσεων.

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INTRODUCTION

Pulmonary hypertension (PH) is a hemodynamic disorder found in several diseases, now defined by elevated mean pulmonary pressure m PAP > 20 mmHg and pulmonary vascular resistance (PVR) ≥ 3 Wood unit measured with right cardiac catheterization (1). Early identification and treatment is needed because advanced disease may be less responsive to the therapy.

The normal values if m PAP at rest is 14.0 ± 3.3 mmHg with an upper limit of 20 mmHg (2), (3). Ranges between 21-24 mmHg should be followed when patients are at risk for developing pulmonary arterial hypertension (PAH).

Severe PH is defined by m PAP ≥ 35 mmHg or m PAP ≥ 25 mmHg with an increased right atrial pressure and/or a decreased cardiac index < 2 L/min/m2.

The classification has been changed in Cologne, Germany, in order to define recommendations for the management of patients presenting with pulmonary hypertension in 2018 (4). Minor changes have been made in clinical classification, especially, in the groups of pulmonary arterial hypertension (group 1), the group of pulmonary hypertension owing to left heart disease (group 2) and the group of pulmonary hypertension with unclear multifactorial mechanisms (group 5). The main categories were not changed (5) (table 1).

Pre-capillary PH due to a primary elevation in the pulmonary system alone (PAH). Post-capillary PH due to a primary elevation of pressure in the pulmonary venous and pulmonary capillary systems (6). The two entities may be present in some patients.

Group 2 consists of PH due to left heart-sided diseases (PH-LHD). It accounts for 48% to 80% of all cases. The most common presentation is in pa-

tients presenting with heart failure and preserved ejection fraction (HFpEF) or reduced ejection fraction (HFeEF). PH-LHD has more severe symptoms, lower exercise capacity and negative impact on prognosis. Especially, patients with HFpEF are older, female, with cardiovascular comorbidities and several components of the metabolic diseases. This condition is defined an m PAP ≥ 20 mmHg and pulmonary wedge pressure >15 mmHg. The presence of PH indicates advance disease with poor prognosis especially when right ventricular failure is presented. PH is due to heart failure (HF) of both systolic and diastolic dysfunction or HF caused by left-sided valvular disease.

Two subgroups are recently recognized. The first group is used to refer in isolated post-capillary PH (Ipc-PH) from passive transmission of increased left-sided filling pressures to the pulmonary circulation. The second subgroup refers to combined post- and pre-capillary PH (Cpc-PH) with overlying pulmonary vascular disease. The survival rates are lower in Cpc-PH patients with acute decompensation of heart failure than in those with Ipc-PH.

Echocardiography is an important diagnostic tool, but right cardiac catheterization remains the gold-standard for the diagnosis. The left cardiac catheterization could be also helpful to phenotype the PH-LHD. Cardiac magnetic resonance imaging is an emerging, alternative diagnostic tool for the disease.

No data support the use of PAH specific therapies in PH-LHD that may be harmful. The current guidelines suggest to treat the underlying cause. Exercise training seems to be beneficial with limitations.

Obstructive or restrictive lung diseases and / or hypoxemia refers to group 3 of clinical classification. Chronic obstructive pulmonary disease and diffuse parenchymal lung diseases (DPLD) including idiopathic pulmonary fibrosis and

sarcoidosis present with high incidence of PH. Echocardiography and right heart catheterization are the principal tests for the diagnosis.

Recent guidelines suggest optimal medical therapy of the underlying lung disease, including long-term oxygen therapy in patients with chronic hypoxemia despite the lack of controlled clinical trials. Continuous positive airway pressure can modestly reduce pulmonary artery pressure but there is no data to support decrease in PH or improved outcomes (e.g. Reduced mortality, improved exercise capacity, delayed progression).

CHAPTER 1: CLASSIFICATION

Pulmonary hypertension (PH) is a heterogeneous condition with symptoms including dyspnea and fatigue (7). With the progression of the disease exertional chest pain or syncope, congestion including peripheral edema, ascites and pleural effusions, with overt right ventricular failure, may be present. Often it is confused with other situations such as age, deconditioning or a coexisting or alternate medical condition. It is a harmful condition, that if untreated may lead to death.

As borderline pulmonary hypertension is defined a mean systolic pressure in pulmonary artery (mPAP) of 19-24 mmHg. Studies and programs had shown that there is an association between borderline PH with mortality and hospitalization for adverse clinical outcomes in patients with underlying left heart dysfunction and parenchymal lung diseases.

A new entity called segmental PH, was presented in World Pulmonary Hypertension Symposium in 2013 (Nice, France). This disorder seems to be associated with congenital heart diseases and it shares many similarities with pulmonary arterial hypertension (PAH) (8). Symptoms depend on ventilation to perfusion (V/Q) mismatch of each area of the lung and the development of right heart failure. It's difficult to calculate separate pulmonary artery pressures and vascular resistance in each affected pulmonary segment. More data are required.

Pulmonary arterial hypertension (PAH) is a rare, progressive and life-threatening disorder that in advanced status can evolve in right cardiac failure. Its hemodynamic definition is represented by the presence of pre-capillary PH in the absence of other causes such as PH due to lung diseases or chronic throm-

boembolic PH (CTEPH). It needs continuous monitoring of the patients functional status.

Exercise-induced PH could not be defined in ESC/ERS Guidelines in 2015 (2) but recent studies have identified this entity in left heart diseases with reserved and reduced ejection fraction (LVEF). It is defined by a mean pulmonary artery pressure > 30 mmHg at a cardiac output < 10 L/min and a total pulmonary vascular resistance (PVR) > 3 Woods units at maximum exercise, in the absence of PH at rest (Figure1, 2).

CHAPTER 2: EPIDEMIOLOGY

The true prevalence of PH is difficult to estimate because of the heterogeneity of the disorder. The epidemiology presents differences in the various groups and sub groups. Most studied is group I. Results from the REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) suggests that patients with newly diagnosed PAH are living longer reporting 3-year survival estimates of 69% and 5-year survival estimates of 61.2%. The prevalence ranges from 15-52 cases/million population and the annual incidence from 2.4 to 7.6 cases/million population. The mean age for the females was 36 years. The ratio females/males was 1.7 to 1. PAH affects middle-aged females. A mean age of diagnosis was at 50 years. The median survival from the onset of symptoms to diagnosis was at the 13.6 months.

The Giessen Pulmonary Hypertension Registry –Survival in PH subgroups concluded:

a) similar or slightly better survival for lung diseases- PH (LD-PH) and slightly worse for pulmonary venous hypertension (PVH) in those reported in the literature

b) death was common in PAH, in chronic thromboembolic pulmonary hypertension (CTEPH) due to right heart failure, in LD-PH due to respiratory failure and in PVH due to combined right and left heart failure

c) NYHA (New York Heart Association) (table 2) and 6MWD (6 minute walk distance) were more favorable in idiopathic PAH (IPAH) than PAH associated with connective tissue disease (CTD-PAH)

d) congenital heart diseases (CHD) / Eisenmenger Syndrome and CTEPH were associated with better survival in the 1 group

e) PVH showed poorer survival

f) isolated post-capillary PH (Ipc-PH) and combined pre and post-capillary PH (Cpc-PH) had similar long-term survival

g) ILD had worse outcome in respect to COPD (chronic obstructive pulmonary disease)

h) men prevalence was higher in LD-PH

Other registries showed increased PH and subgroups cases in the elderly: most common PAH, CHD-PAH CTD-PAH, CTEPH (ASPIRE: Assessing the Spectrum of PH identified at a Referral centre), IPAH most common (COMPERA: Comparative Registry of newly initiated therapies for PH).

The conclusions from registries and studies are*:*

1) an increased incidence of CTD-PAH especially in those affected from scleroderma

2) IPAH is present in younger on average patients than other PAH subgroups

3) CHD-PAH has better outcomes

4) A female preponderance is estimated for females in PAH

5) Groups 2 and 3 are the most common and lethal forms of PH

CHAPTER 3: GENETICS AND GENOMICS

Technological advances in genetic sequencing of the coding regions of the genome have been studied for the comprehension of the genetic predisposition in families with PAH (9). Around 70-80% of families with PAH and 10-20% with IPAH, have mutations in BMPR2. The core of the disease conclude the following genes according the level of evidence: BMPR2*;* EIF2AK4*;* TBX4*;* ATP13A3*;* GDF2*;* SOX17*;* AQP1*;* ACVRL1*;* SMAD9*;* ENG*;* KCNK3*;* CAV1

BMPR2 is highly expressed on the pulmonary vascular endothelium where it forms a complex with receptors ALK1 and ALK2.

CAV1 is a constituent of caveloae, highly expressed in endothelial cells. In caveloae maybe start the BMP signaling. The penetrance in males is around 14%, while in females is around 42%. The greater penetrance in females may be due to oestrogen metabolism. Furthermore, inflammatory factors such as tumor-necrosis factor -a, lipopolissaride and lipoxygenase -5 can induce in PAH in genetically modified mice. However, another predisposition factor can be the somatic mutation within muscular cells that follow the DNA damage.

Genetic education and counselling should be performed prior to genetic testing for PAH to address the complex issues of incomplete penetrance, questions of surveillance for genetically at-risk family members, reproductive questions, concerns about genetic discrimination, as well as psychosocial issues of guilt and blame that can accompany genetically based diseases.

The genetic information is crucial for targeted therapies and prognosis. For example, HPAH associated with *BMPR2* or *ACVRL1* mutations presents at a younger age, with more severe hemodynamic abnormalities, and a very low

probability of acute vasoreactivity, as well as reduced survival in the current treatment era.

Patients with a heritable form of PVOD are also younger at presentation than non-mutation carriers, but there is no significant difference in the event-free survival at 3 years.

CHAPTER 4: PYLMONARY HYPERTENSION IN LEFT HEART-SIDED DISEASES

The clinical classification of pulmonary hypertension (PH) is categorized in in five groups in Nice, 2013. Left heart diseases (LHD) complicated by pulmonary hypertension are designated Group 2. This group has not been changed recently, in 2018, but the entity of congenital/acquired pulmonary vein stenosis has been added. Left heart-sided diseases are the most common form of PH. They have a one-year mortality of 41%.

The pulmonary vein stenosis is a rare disease with high morbidity and mortality in advanced stages (10). It consists in a progressive lumen size reduction of one or more pulmonary veins, that can cause, if hemodynamically significant, an increase of lobar capillary pressure leading in dyspnea, cough and hemoptysis. In the past, it was linked to congenital heart diseases in childhood and mediastinal processes (e.g. tumours) in adults, but at present, it is linked with the radiofrequency ablation for atrial fibrillation The prevalence after interventional pulmonary vein isolation (PVI) for atrial fibrillation is 0.2-0.4% and has become less frequent .

The task force on pulmonary hypertension associated with left heart diseases proposed another hemodynamic classification in 2018: 1) Ipc-PH with values of PAWP>15 mmHg and m PAP>20 mmHg and PVR<3Wood unit. 2) Cpc-PH with values of PAWP>15 mmHg and m PAP>20 mmHg and PVR≥3Wood unit.

Heart failure with reduced and preserved ejection fraction and left-sided valvular diseases is the most common cause of pulmonary hypertension.

The most common mechanism in PH-LHD consists in passive transmission of elevated left heart filling pressures to the pulmonary circulation. This is determined by the diastolic function of the left ventricle (LV) and maybe by an exercise-induced mitral regurgitation and loss of left atrial compliance. The second mechanism is pulmonary arterial vasoconstriction and remodeling associated with increased pulmonary vascular resistances (PVR), due to an imbalance between a decreased nitric oxide (NO) availability and an increased endothelin expression, as described in the “mitral lung (11).

Right ventricular failure is the result of changes in pulmonary arterial, capillary and venous circulation. The capillary stress failure resulting from edema and disruption of the alveolar capillary barrier conduce to repetitive cycles of injury and repair (13). The vascular endothelial dysfunction, the increased pulmonary vascular tone, the pulmonary vascular and alveolar wall remodeling and the proliferation of myofibroblasts are, partially, part of a protective mechanism that leads to a restrictive lung syndrome and impaired gas exchange, contributing to PH (Figure 1).

In addition, central to endothelial dysfunction in PH is an imbalance of the vasodilator nitric oxide (NO) and the vasoconstrictor endothelin-1 (14). Patients with Cpc-PH are known to undergo pulmonary vascular remodeling including endothelial dysfunction. Genetic polymorphisms affecting the NO signaling pathway, may influence susceptibility to these patients. The right ventricular failure is associated with decreased exercise capacity and poor prognosis.

The current hemodynamic classification of PH-LHD consists in 2 subgroups.

The isolated post-capillary PH (Ipc-PH) and the combined post- and precapillary PH (Cpc-PH). Patients usually have Ipc-PH defined by m PAP

≥25mmHg and a pulmonary arterial wedge pressure (PAWP) >15 mmHg (Table 5). Both are characterized by elevated pulmonary arterial wedge pressure>15 mmHg (PAWP).

This definition has been recently challenged. In a recent study, has been introduced the term of intermediate PH-LHD with hemodynamic features between the Ipc-PH and Cpc-PH with DPG < 7 mmHg or PVR < 3 WU

(24). Data from three groups of patients (Ipc-PH, the intermediate group and the Cpc-PH), have shown that patients with Ipc-PH have a better prognosis compared with patients with Cpc-PH and with patients with isolated increase of PVR or DPG. Pulmonary vascular resistance has a better predictive value than DPG in patients with PH-LHD (15). The invasive measures of Ipc-PH conclude a diastolic pulmonary pressure gradient <7 mmHg (DPG), a transpulmonary gradient (TPG) <12mmHg and a pulmonary vascular resistance (PVR) ≤ 3 Wood.

In Cpc-PH the pre-capillary component is caused by the presence of a pulmonary vascular disease. It is associated with severe PH .

The clinical classification of PH-LHD is based on the underlying type of LHD. The new ESC guidelines on heart failure distinguish between HFrEF (EF<40%), heart failure with mid-range EF (HFmEF EF; 40-49%) and HFpEF (EF≥50%) (14) (table 6).

In HFrEF, the prevalence of PH in RHC was between 40% and 75%. In patients with HFpEF, the prevalence of PH was 36% to 83%, based on echocardiographic criteria. In HFrEF, elevated PAP and reduced systolic RV function was associated with prognosis. In HFpEF, right ventricular dysfunction (measured as TAPSE: tricuspid annular plane systolic excursion) or RV-FAC (right ventricular fractional area change) associated with increased PAP, was also associated

with high mortality. The clinical classification of PH-LHD is based on the underlying type of LHD.

Valvular heart disease

1) Mitral stenosis

The improvement of PH after the valve defect illustrates the reversibility nature of PH-LHD.

2) Mitral regurgitation

Functional mitral regurgitation is a frequent cause of PH with increased mortality. Surgical or interventional treatment, including catheter-based approaches such as MitraClip or CardioBand, leads to improvements in pulmonary hemodynamics. Recent data from TRAMI registry have shown that even moderate PH affects post-precedural survival in patients undergoing MitraClip therapy.

3) Aortic stenosis

Symptomatic aortic valve stenosis is associated with PH in up to 65%. Preoperative PH (usually defined as PASP >60 mmHg) in surgical valve replacement increases the complications and have long-term prognosis. In some cases, with severe aortic stenosis, PH may persist even after successful valve correction. Pre-interventional PH in TAVI (transcatheter aortic valve implantation) is associated with a poor prognosis.

4) Congenital/acquired left heart inflow/outflow tract obstructions and congenital cardiomyopathies

Congenital conditions prone to develop post-capillary PH include congenital mitral stenosis, Shone complex (combination of left heart deformities and the aortic arch), cor triatriatum, transposition of the great arteries after atrial switch with baffie stenoses, congenital stenosis of the left ventricular outflow tract and

aortic isthmus stenosis. Targeted PAH therapy is not indicated in Ipc-PH patients.

Measures by right catheterization conclude elevated DPG, elevated TPG, elevated PVR, pronounced ventilator responses to exercise maybe because of more exercise-induced hyperventilation and less exercise oscillatory breathing (EOB) (15), decreased pulmonary arterial compliance, depressed right ventricular (RV) ejection fraction (EF) and high morbidity and mortality of patients with Cpc-PH respect to Ipc-PH. It shares similarities with PAH.

Patients with pre-capillary PH have higher hyperventilation but no EOB. Prevalence of EOB decreased from Ipc-PH to Cpc-PH to PAH (16). Patients with Cpc-PH may have worse hemodynamics than those with Ipc-PH and distinct alterations of ventilator control, consistent with more exercise-induced hyperventilation and less EOB (17).

Misdiagnosis PH-LHD as PAH may cause detrimental effects from inappropriate therapies because of different pathophysiology.

In PH-LHD, especially in heart failure (HF), the endothelial dysfunction is supported by an increase of endotelin-1 activity and the imposed nitric oxide-dependent vasodilatation.

An underestimation of left heart filling pressures can be seen in diuretics with normalized PAWP.

The heart failure with preserved or reduced ejection fraction may present similarities with pulmonary veno-occlusive disease (PVOD) (18). The PH is associated with global pulmonary vascular remodeling and the severity of PH correlates with venous and small indeterminate vessels thickening, similar to the pattern observed in PVOD.

The risk stratification of patients remains of poor data. Studies related to identification of high risk patients have included increases of TPG and DPG.

TPG is not always correlated with pulmonary vasculature remodeling.

The normal values of DPG in normal heart are greater than zero.

A study published on JACC (2015) has proved that an elevated DPG cannot determine a worse survival in heart failure.

A study published in Circulation HF (2018), had added that pulmonary arterial elastance and pulmonary arterial compliance can predict mortality better than PVR or TPG, including patients with HFpEF, HFrEF and PH with a normal pulmonary vascular resistance.

Several studies have tried to show the impact of different markers on survival. A past study supports, also, the relevance of pulmonary arterial capacitance in mortality (19). However, another study suggested the pulmonary vascular compliance (PCa) as the stronger predictor of survival in HF with reduced or preserved ejection fraction rather DPG (20). It remains controversial the specific marker that can predict the high risk groups in Cpc-PH.

1. Pulmonary hypertension in left heart diseases versus pulmonary arterial hypertension

PH-LHD when presented is associated with advanced disease, reduced functional status, poor prognosis and high mortality.

The similarities with PAH seems to be connected because of genetic polymorphism commune in both.

Tufik R. Assad et. al. have supported that genetic architecture and pathways may be present in the lung, involving the vascular remodeling, than in other tissues and the possibility of pathophysiological overlap between PAH and Cpc-LDH in the development of pulmonary vascular disease was high.

The most interesting pathways have included actin binding, basement membrane, extracellular matrix and major histocompatibility complex class II proteins. 75 exonic single-nucleotide polymprphisms (SNPs) were associated, including 2 genes responsible for PAH progression (COL 18A1) and modulation (SMCR7). The clinical presentation, the echocardiography findings and other features may suggest the presence of PH –LHD (table 7).

The algorithm that differentiates pulmonary arterial hypertension and pulmonary hypertension with left heart disease is indicated in figure 2.

The indications for right cardiac catheterization in PH-LHD should be performed in stable clinically patients (table 8).

On the other hand, patients with pre-capillary PH and cardiopulmonary comorbidities and risk factors for left heart disease, specific criteria were introduced (table 9).

2. The Right Ventricle

Despite his active participation in cardiopulmonary disease, the evaluation of the right ventricle (RV) remains challenging, because of its unique geometry and the differences from left ventricle.

Some patients may develop advanced PH and RV impairment in left-sided HF than others.

A predisposition for pulmonary vascular disease may be responsible but a transmission from the LV phenotype to a RV phenotype characterized by dilation and function impaired superimposed on the LV phenotype, is possible (21).

The ultimate may be a logical mechanism in HFpEF in presence of RV dysfunction found in more advanced stages. The rates of mortality in RV phenotype seem to be high.

In HFpEF pulmonary hypertension and RV dysfunction have a central role. It seems that there is a straight correlation between RV and pulmonary circulation (PC) (RV coupling). However, RV dysfunction seems to be connected with the left atrium. A non-compliant left atrium increases the systolic PAP. The impaired left atrium seems to be the hemodynamic trigger for RV-pulmonary artery (RV-PA) uncoupling and exercise ventilation inefficiency in HF. Altered RV coupling and pulmonary vascular remodeling is associated with Cpc-PH (22). In chronic heart failure (HF), Cpc-PH is rare and characterized by younger age, chronic obstructive pulmonary disease and worse RV coupling (23). Prognostic information may be more related with worsening of RV-PA coupling than hemodynamic phenotyping (24). The use of the tricuspid annular plane systolic excursion (TAPSE)

and pulmonary artery systolic pressure (PASP) dominate on the ratio of RV systolic elastance (Ees) and arterial elastance in determining the RV contractility and the afterload.

In a recent study, pulmonary arterial elastance defined as the ratio of stroke volume to pulmonary pulse pressure, was the best predictor of mortality in PHH-LHD in HFpEF.

Furthermore, although TAPSE and PASP are indicators not used currently in PAH, it seems that offer clinical information about the RV-PC coupling.

Their estimation made by older and novel echocardiographic techniques, presents many limitations: give information about the longitudinal wall motion of RV, it is high-angle and operator-dependent, not confident results in presence of severe tricuspid valve regurgitation and not defining the contractile curve of RV.

Ees and Ea have their limitations such as instantaneous recordings of RV pressure and volume through stimuli p.e. Valsalva maneuver is not always easy at the bedside. But the ratio TAPSE/PASP remains crucial for RV impairment.

CHAPTER 5: PULMONARY HYPERTENSION IN LUNG DISEASES

Pulmonary hypertension due to pulmonary disease is group 3 of the clinical classification. This group is the second common form of PH. It carries a one-year mortality of 46%. It is associated with obstructive or restrictive lung disease and/or conditions that cause hypoxemia (obstructive sleep apnea, alveolar hypoventilation disorders). It is a complication of COPD, interstitial lung disease and combined pulmonary fibrosis and emphysema.

In 2018, new terms have been introduced: PH-COPD, PH-IPF, PH-CPFE and severe PH-COPD, PH-IPF, PH-CPFE. Non severe disease refers to lung diseases with an m PAP≥25 mmHg, severe disease to those with an m PAP≥35 mmHg or an m PAP≥20mmHg and decreased cardiac output. (25).

The definitions and management of PH due to chronic lung disease are listed in table 11.

Chronic obstructive lung disease

Up to 90% of patients have m PAP >20 mmHg. Approximately 1-5% of COPD patients have m PAP >35-40 mmHg at rest. Exercise PH in COPD may be due to comorbid left heart disease. There is a cluster of patients representing a “pulmonary vascular COPD phenotype”, characterized by less severe airflow limitation, normo- or hypocapnia and a cardiovascular exercise limitation profile. The vascular lesions seem in COPD-PH are similar to those in IPAH. An increased pulmonary artery diameter, as seen in computed tomography (CT) scan, predicts hospitalization due to acute COPD exacerbation.

Combined pulmonary fibrosis and emphysema

It is defined by the simultaneous presence of emphysema in the upper lobes and fibrosis in the lower lobes on chest CT. It is associated with poor survival.

From several studies results that group 3 patients are older, have comorbidities, and more severe functional and hemodynamic impairment. This may be explained by the burden of parenchymal lung disease and the pulmonary vascular disease. Survival rates were lower in patients with idiopathic pulmonary fibrosis (IPF), non-IPF ILD and combined pulmonary fibrosis and emphysema (CPFE).

From COMPERA registry results worse survival in ILD-PH than in idiopathic pulmonary arterial hypertension (IPAH). Patients with combined pulmonary fibrosis and emphysema (CPFE) are particularly prone to the development of PH. Echocardiography and right heart catheterization (RHC) are the principle modalities for the diagnosis. PH therapy in severe lung disease did not improve the 6MWD or the functional class, but neither was deteriorated, in contrast to IPAH which showed improvement in 6MWD and the N-terminal pro-brain natriuretic peptid (NT-proBNP).

Chronic exposure to hypoxia may promote the development of arterial remodeling and the development of venous arterialization in advanced COPD (23). The venous remodeling is correlated negatively to DLCO which maybe an independent predictor of mortality in COPD-PH.

The severe PH group includes a minority of patients with pulmonary vascular remodeling and exhausted circulatory reserve. Dyspnea on exercise disproportionate to function pulmonary tests, low carbon monoxide diffusion capacity and rapid decline of arterial oxygenation upon exercise are the principle clinical features in patients with poor prognosis.

RHC, the gold standard for PH diagnosis, should be performed in patients with chronic lung disease when

1) evaluation for lung transplantation is deemed necessary;
2) clinical worsening and progressive exercise limitation is disproportionate to ventilator impairment;
3) progressive gas exchange abnormalities are disproportionate to ventilator impairment;
4) an accurate prognostic assessment is deemed to be critical;
5) severe PH is suspected by noninvasive measures and further therapy or inclusion in clinical trials or registries are being considered; and
6) there is suspicion of left ventricular systolic/diastolic dysfunction and categorization of the pulmonary artery occlusion pressure might alter management (adapted from Nathan and Cottin)

Lung diseases (in particular COPD) are common conditions, and development of PAH in such patients may not necessarily be the result of these diseases (definition group 3 PH patients) but may be coincidental.

When there is uncertainty in the classification of a patient with lung disease and PH to group 1 (PAH) or group 3 (PH caused by lung disease), the patient should be referred to centers with expertise. Some suggested criteria for discrimination between group 1 and group 3 are including in table 3.

Diverse mechanisms are involved in the pathogenesis of pulmonary hypertensive vasculopathy in the setting of parenchymal lung diseases and/or hypoxia.

Pulmonary vasoconstriction, triggered by hypoxia, represents the main pathogenetic mechanism in PH in high-altitude dwellers and in patients with sleep disordered breathing.

The vascular changes seen in healthy high-altitude natives are reversible and they may resemble the pulmonary vascular remodeling in COPD patients (26).

The vasoconstriction leads to structural changes in lung vasculature, affecting mostly the small pulmonary arteries. In COPD, hypoxia, the exposure to tobacco smoke and the loss of pulmonary vessels contribute to pulmonary hemodynamic impairment, through vascular remodeling. PH in usual interstitial pneumonia (UIP) is characterized by structural changes involving pulmonary vessels both within the fibrotic areas and outside fibrosis.

The biological mechanisms underlying vascular remodeling in UIP are incompletely understood and encompass an altered balance between angiostatic and angioproliferative mediators and the effects of both oxidative and paracrine molecules perturbing vascular cell homeostasis.

The occurrence of PH in parenchymal lung disease complicates the therapeutic attitude and requires the guidance of specialist consultation.

CHAPTER 6: PROGNOSIS

The 12-month mortality rates for PH-LHD, with prediction of mortality including older age, male sex, right ventricular (RV) dysfunction, renal disease and decreased functional class.

The injection fraction of left ventricle and the injection fraction of right ventricle have been used for the prediction of survival rates.

A cohort that has concluded patients with heart failure (HF) and reduced ejection fraction of the left ventricle (LVEF) ≤ 40%, the risk of death was high.

The 6 month survival rates were lower in Cpc-PH in patients with acute decompensated HF than those with Icp-PH. Chronic heart failure presents, rarely, Cpc-PH. Worse outcomes can be explained by the mismatch of right ventricle and pulmonary circulation (RV coupling). Studies based on the ejection fraction of the right ventricle have proved that increased mean PAP > 20 mmHg and low RVEF < 35%, had poor prognosis than normal PAP with preserved or low RVEF or high PAP with preserved RVEF. In HFpEF complicated by PH in left-sided heart diseases, RV systolic dysfunction was associated with high mortality than PASP > 47mmHg.

REVEAL registry can predict using a risk score, the survival in patients with PAH. Untreated patients had one-year survival rate of 85%, three year survival of 68%, five –year survival of 57% and seven-year survival rate of 49%. The registry is, also, used in newly diagnosed disease.

The risk score is the sum of points derived from clinical data including 1 subgroup, demographics and comorbidities, functional class, vital signs, 6MWD, brain natriuretic peptide level, echocardiogram, pulmonary function tests, and RHC findings. This risk score calculates survival only and should not be used to make decisions for treatment. A single – center setting study showed a strong association between low diffusion capacity of the lung for carbon monoxide (DLCO) and HFpEF-PH in pre-capillary component.

A low DLCO was found in almost one-half of the patients, especially and it was associated with high mortality.

CHAPTER 7: PULMONARY HYPERTENSION AND COMORBIDITIES

Patients with diabetes mellitus and pulmonary arterial hypertension are more susceptible in right ventricle remodeling and dysfunction as measured by pulmonary artery stiffness, pulmonary arterial elastance, pulmonary artery capacitance band pulmonary arterial resistance because of an increase in right ventricular overload (27).

Data from patients with central apneas, proved that the Cheyne-Stokes respiration (CSR) may influence the increase of pulmonary artery pressure and the RV remodeling through the hypoxia/hypercapnia cycles chemoreflex activation independently of the LV systolic and diastolic dysfunction.

The obese population is in continuous increasing worldwide. The presence of obesity HFpEF is common and produces many cardiovascular complications. It seems to be a benign form of heart failure with a specific phenotype requested targeting therapies (28).

A study published in 2018 correlates PAH in preserved RV function with lower extremity venous insufficiency through variable scores and conclude that the degree of venous insufficiency is in interaction with mean pulmonary arterial pressure (29). There is a lack of evidence in the interrelation between the two diseases.

CHAPTER 8: TREATMENT

PAH is a rare, debilitating disorder that can cause right heart failure and death.

The main targeting therapies, understanding in part the pathophysiology of PAH were epoprostenol and derivates, endothelin receptor antagonists and phosphodiesterase 5 inhitors. The treatment algorithm has been changed in summer 2016, because the patients with PAH were older, with cardiac comorbidities and were presented with IPAH. For younger patients without comorbidities, nothing has been changed.

Low or intermediate risk patients should be treated with endothelin receptor antagonists and phosphodiesterase 5 inhitors or soluble guanylate cyclase stimulators. In high risk patients a triple combination including a subcutaneous or intravenous prostacyclin, should be used.

Patients who presents PAH and cardiac diseases, initial monotherapy is recommended. The combined therapy should be personalized. The targeting therapies for PAH seems that cannot be used to most patients in this group as multicentre randomized trials have shown.

Patients presented with left heart disease and development of PH, should be managed treating the underlying cause (table 10). This relates, primarily, to the correction of valve defects, and guideline-directed treatment of HFrEF. Also, comorbidities that may cause PH should be treated. The vasoreactivity testing can be used in the diagnosis of PH but it can’t be used in PH-LHD.

A recent registry has shown improved exercise capacity in treatment with phosphodiesterase type 5 inhibitorsin in idiopathic PH and in atypical PAH. Another registry showed improved hemodynamics in Cpc-HF before heart transplantation treated with sildenafil. Similar, the improvement of pulmonary vascular distensibilty, defined as, the percent increase in pulmonary vessel diameter per mmHg increase in pressure, seems to be present under treatment with short-term PDE5 inhibitor therapy (30). However, a few trials (SIOVAC trial), haven't shown benefit with sildenafil. This may be due to lung vasodilation which increases pulmonary venous return and LV filling pressure and increased ventilation-perfusion mismatching. In the MELODY trial, macitentan showed adverse events and fluid retention not Improving the endpoints (PVR, PCWR, cardiac index, and NT-pro-BNP). Endothelin receptor antagonists and prostacyclin analogues have shown short-term changes in henodynamics but no clinical benefit.

In case of advanced HF, elevated PVR, has been a contraindication to heart transplantation because the increase in RV afterload was prohibitive for RV graft. The recent 2016 guidelines for heart transplantation of the International Society for Heart and Lung Transplantation recommend to perform RHC before heart transplantation in order to measure the m PAP and PVR.

Treatment of the underlying disease is indicated in all patients with group 3 PH. Therapeutic approaches studies note that treatment with vasodilators, such as calcium channel blockers, is not recommended because these drugs may impair gas exchange due to the inhibition of hypoxic pulmonary vasoconstriction and because they are not effective in long-term

studies. The oxygen supplemental therapy improves survival in COPD and PaO2<55 mmHg. Predictors of a long-term response to continous oxygen include a decrease of m PAP > 5 mmHg after 24 h of 28 percent oxygen and a high peak consumption (VO2) after symptoms.

Strategies such as continuous positive airway pressure, can reduce PAP, but there is no evidence for reduction of PH or for less harmful outcomes (e.g. reduced mortality, improved exercise capacity, delayed progression).

Group 4 should be treated with anticoagulation or surgical thromboarterectomy in selected patients. Perioperative mortality is < 10% in specialized centers. The surgical risk is increased in presence of PAH and right ventricular dysfunction because of complications and death when undergoing anesthesia, mechanical ventilation and major surgery. The major complications are emerging in emergency surgery, in increased atrial pressure > 7 mmHg, in 6MWD ≤ 399 meters and the perioperative use of vasopressors.

Oxygen therapy should be considered in all patients with PH combined with hypoxemia in Group 5. 1-4 L/min via nasal prongs should be used to maintain oxygen saturation > 90% at rest and if possible in exercise and sleep.

The conventional medical therapies for PH must be personalized for groups 3-5 after careful weighting the risks versus benefits.

CHAPTER 9: REHABILITATION

PH is a heterogeneous disease with diverse phenotypes affecting lung circulation.

The main self-limiting clinical impact is breathlessness during the daily activity that provokes social and psychological consequences. Several studies had proved the safety of exercise programs for improvement of functional status and of quality of life even in end-life disease (31).

Physiotherapy interventions should be able to support newly-diagnosed patients, manage their symptoms, to stabilize better health outcomes in chronic patients from the diagnosis to the end-stage disease, promote their self-management during the daily life, personalize specific strategies for patients, offer rehabilitation before any surgery. Physical activity and regular exercise is important in chronically ill patients, more predisposed in deconditioning. The aerobic exercise is the most important strategy for cardiopulmonary diseases. The beneficial effect is dose and time responsive and its application requires a prescription to adjust the frequency, duration and intensity of)exercise based on the disease severity (33). Most exercise regimens have a constant time and a slow build up of exercise intensity.

The patient evaluation before starting the aerobic exercise training includes clinical and psychological assessment, current and past medical history (including activity), function and exercise habits, and the assessment of mental status and cognitive ability.

It must be noted if cardiopulmonary instability is present. Information about medications, impediments to exercise such as arthritis, deformities and surgical wounds is important.

Spirometry for assessing the severity of the lung disease and echocardiography for the severity of cardiac disease must be carried out. Several functional tests to evaluate the functional status are available: the cardiopulmonary exercise testing, the 6MWD, and the incremental shuttle test. An adequate warm-up and cool-down period is highly recommended especially in ischemic heart disease. The test must be stop when symptoms are present for the safety of the patient paying attention to indications and contraindications of the training. Training large muscle groups is more effective. The training should have uniform time, about 30 minutes at least three times per week. Cardiac surgery patients should ensure stability of the postsurgical wound healing. Patients with COPD and reactive airways should use their bronchodilator before staring especially if the test shows dynamic hyperinflation.

If forced expiratory volume (FEV1) is severely reduced the endurance time should be reduced.

1. Cardiac rehabilitation

Exercise training has been shown to be safe in cardiac rehabilitation (CR) (34).

Patients with an implantable cardioverter-defibrillator (ICD), exercise heart rates should not reach higher than 10-15 beats the ICD tachycardia threshold.

The contraindications for CR conclude unstable angina, uncontrolled hypertension, orthostatic blood pressure, significant aortic stenosis, uncontrolled atrial or ventricular tachycardia, uncontrolled sinus tachycardia, uncompensated HF, third-degree atrioventricular block without pacemaker, active pericarditis or myocarditis, recent embolism, acute thrombophlebitis, acute systemic illness or fever, uncontrolled diabetes mellitus, severe orthopedic conditions, metabolic conditions as thyreoiditis, hypokaliemia, hyperkaliemia, or hypovolemia (until treated).

Management of exercise-induced desaturation in congestive heart failure (CHF) characterized by impaired oxygen delivery to working muscles, can be treat by prescription of oxygen during training in normoxemic patients with desaturation level below of 85%. In CHF weight and fluid control have to be adjusted during rehabilitation.

In patients with coronary disease an antiatheromatous diet should be performed. CR and PR should be accompanied by smoking cessation, igiene-diet education and optimal medical therapy.

In symptomatic patients who experience dyspnea, fatigue and reduced functional status improving quality of life, is the treatment goal.

Aerobic, interval and strength training offer benefits in CHF.

The inspiratory muscle training is not recommended and should be limited in patients who cannot perform a holistic exercise. In the absence of a maintenance program, the benefits seem to diminish over 6-12 months and a long-term program is needed. In advanced stages of HF, the degree of training is lower. So low-intensity inspiratory and peripheral resistance muscle training improves inspiratory and peripheral muscle strength and walking distance. The moderate intensity resistance training improves expiratory muscle strength and New York Heart Association (NYHA) of the patient.

2. Pulmonary rehabilitation

It is defined by the American Thoracic society and the European Respiratory Society as a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to exercise training, education, and behavior change designed to improve physical and psychological condition of people with chronic obstructive respiratory disease (COPD) but also in other pulmonary diseases different than COPD promoting the long-term adherence to health enhancing-behaviors (34).

In general, improve symptoms, quality of life, pulmonary function and health care utilization. The 6-minute can be used to stratify patients with COPD for clinical trials and interventions aiming modify exacerbations, hospitalizations or death. Comparing the linear incremental treadmill protocol with cycle ergometry the responses are similar in severe COPD. However, the treadmill protocol is advantageous because of the greater desaturation respect the ambulation. It is clear that the debilitated patients need shorter times in treadmill protocols.

A study published in Jama (2016), defined that hospitalized patients with acute respiratory failure, received standardized rehabilitation therapy, didn't present a decrease in hospital length of stay (LOS) compared with usual care. The results consisted in the similarity of LOS in both groups, the similarity in duration of ventilation, the absence of effect at 6 months for handgrip and handheld dynamometer strength.

Some recent studies showed no benefit on hospital readmissions and mortality explained by the extensiveness rehabilitation programs and by the methodological quality of the included studies.

More studies need to stabilize the components of the rehabilitation programs in exacerbations in unstable COPD. In obese patients with COPD, different exercise modality has similar responses in ventilation, operating lung volumes and dyspnea intensity during incremental walking and cycling exercise. The treadmill testing was associated with higher oxygen uptake, lower ventilator equivalent for oxygen and greater oxyhaemoglobin desaturation at a given work rate. Cycle testing was associated with a higher respiratory exchange ratio, earlier ventilator threshold and greater leg discomfort. A highly supervised program in PAH, in expert centres, improves Qol, symptoms, exercise capacity and haemodynamics in selected treated patients. Skeletal muscles, cardiopulmonary system and immune system benefit from the programs. It is crucial to avoid strenuous exercise and exhaustion because of adverse effects like pre-/syncope, arrhythmia, respiratory infections. PR benefits people with chronic respiratory disease, yet few eligible people enroll. Patients with lung disease are often unaware of or lack access to PR. Important healthcare disparity should be addressed.

A prospective multicentre study shows that electrical myostimulation on top of exercise training does not add improvement in exercise capacity.

Especially the effect of quadricipital electrostimulation has not yet been evaluated.

CONCLUSIONS

PH is a serious condition when advanced, especially when it is misdiagnosed and untreated.

Left heart diseases (group 2) that cause pulmonary hypertension, are divided in two subgroups. The first subgroup is defined isolated pre-capillary pulmonary hypertension that is due to a backward transmission of elevated left filling pressures to the pulmonary circulation. The second is the combined pre- and post-capillary pulmonary hypertension. The latest is owning to elevated pressures in the pulmonary venous and capillary system (pulmonary venous hypertension). Recent changes that have been suggested, aim for better prognosis and treatment of patients. Congenital/acquired pulmonary vein stenosis has been added in clinical classification.

Especially the heart failure with preserved ejection fraction is a disease of aging patients. Right ventricular coupling, the mismatch between the right ventricle and the pulmonary circulation, seems to be essential in the pathogenesis of PH in patients with combined pre-capillary PH. Also, the development of right ventricular failure is responsible for the severity of the disease. The studies have shown that the majority of patients, had the commune comorbidities as in left heart disease, such as cardiovascular diseases, arterial hypertension, diabetes, atrial fibrillation and renal failure.

The patients with combined pre- and post-capillary pressure seem to have lower survival rates.

Surgical or interventional treatment, leads to improvements in pulmonary hemodynamics in mitral regurgitation.

Pre-operative PH in surgical valve replacement increases the complications and have long-term prognosis. In some cases, with severe aortic stenosis, PH may persist even after successful valve correction.

The patients presenting with a lung disease (group 3), are older, they have comorbities and severe functional impairment. The burden of parenchymal disease and the presence of pulmonary vascular disease, seem to be the main causes for the severity of PH mediated by the vascular remodeling. Several studies have proved worse outcomes for the interstizial lung disease, such as, the combined pulmonary fibrosis and emphysema respect to COPD. These diseases are the second form of PH that may cause mortality in about half patients. Oxygen supplementation therapy seems essential, but there is a lack of evidence for other strategies that can improve quality of life and reduce poor outcomes.

Cardiopulmonary rehabilitation seems to be beneficial in both groups 2 and 3 improving the functional status and the quality of life in most of the patients.

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TABLES-FIGURES

Table 1: **Detailed clinical classification of pulmonary hypertension**

1. Pulmonary arterial hypertension	• **Idiopathic** • **Heritable (BMPR2 or other mutation)** • **Drugs or toxins induced** • **Associated with** • **Connective tissue disease** • **HIV infection** • **Portal hypertension** • **Congenital heart disease** • **Schistosomiasis**
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	• Idiopathic • Heritable (EIF2AK4 or other mutation) • Drugs/toxins/radiation induced • Associated with connective tissue disease or HIV infection
1″. Persistent pulmonary hypertension of the newborn	
2. Pulmonary hypertension due to left heart disease	• Left ventricular systolic dysfunction • Left ventricular diastolic dysfunction • Valvular disease • Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies • Congenital/acquired pulmonary vein stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia	• **Chronic obstructive pulmonary disease** • **Interstitial lung disease** • **Other pulmonary diseases with mixed restrictive and obstructive pattern** • **Sleep-disordered breathing** • **Alveolar hypoventilation syndromes** • **Chronic exposure to high altitude** • **Developmental lung diseases**
4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions	• Chronic thromboembolic pulmonary hypertension • Other pulmonary artery obstructions • Angiosarcoma • Other intravascular tumours • Arteritis • Congenital pulmonary artery stenosis • Parasites (hydatidosis)
5. Pulmonary hypertension with unclear and/or multifactorial mechanisms	• Haematological disorders (chronic haemolytic anaemia, myeloproliferative disorders, splenectomy) • Systemic disorders (sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis) • Metabolic disorders (glycogen storage disease, Gaucher disease, thyroid disorders) • Others (pulmonary tumoural thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure with/without dialysis, segmental pulmonary hypertension)

BMPR2: bone morphogenic protein receptor type 2, EIF2AK4: eukaryotic translation initiation factor 2 alpha kinase 4.

Table 2: The New York Heart Association Functional Classification

NYHA Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Table 3: Hemodynamic definitions of post-capillary pulmonary hypertension (PH).

Definition	Characteristics[a]	Clinical groups
Post-capillary PH	mPAP≥25mmHg PAWP>15mmHg	• PH due to left heart disease • PH with unclear and/or multifactorial mechanisms
Isolated post-capillary PH (IpcPH)[c]	PVR≤3 WU[b] (and/or DPG<7mmHg and/or PA_C≥2.3ml/mmHg)	
Combined post- and pre-capillary PH (CpcPH)[c]	PVR>3 WU[b] (and/or DPG≥7mmHg and/or PA_C<2.3ml/mmHg)	

DPG: diastolic pressure gradient, PA_C: pulmonary artery compliance, mPAP: mean pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, PVR: pulmonary vascular resistance, WU: Wood units.

a. All values measured at rest.
b. Wood units are preferable to $dyn \cdot s \cdot cm^{-5}$.
c. Change from original guidelines.

Table 4: Clinical classification of pulmonary hypertension due to left heart disease. (Nice group 2)

Pulmonary hypertension due to left heart disease
Left-ventricular systolic dysfunction (heart failure with reduced ejection fraction; HFrEF)
Mild left-ventricular systolic dysfunction[a] (heart failure with mid-range ejection fraction; HFmrEF)
Left-ventricular diastolic dysfunction (heart failure with preserved ejection fraction; HFpEF)
Valvular heart disease (VHD)
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Congenital/acquired pulmonary vein stenosis

Table 5: Factors which suggest the presence of pulmonary hypertension due to left heart disease (PH-LHD) in patients with suspected pulmonary hypertension

Clinical presentation	Echocardiography	Other features
Age>65years **Symptoms of left heart failure** **History of CHD**	• Structural left heart disease: – Left-sided valvular heart disease – LA enlargement (>4.2cm) – Bowing of the IAS to the right – LV dysfunction (systolic / diastolic) – Concentric LV hypertrophy and/or increased LV mass – Doppler indices of increased LV filling pressure: – Increased E/e′ – >Type 2–3 mitral flow abnormality	• ECG: – LVH and/or LAHB – AF/Afib – LBBB – Presence of Q waves – Absence of “RV strain” – Other imaging: – Kerley B lines – Pleural effusion – Pulmonary edema – LA enlargement
Features of the metabolic syndrome	Absence of: • RV dysfunction • Mid-systolic notching of the PA flow • Pericardial effusion	
History of heart disease (previous or current)		
Atrial fibrillation (persistent/permanent)		

AF/Afib: Atrial flutter/atrial fibrillation, CHD: coronary heart disease, IAS: interatrial septum, LA: left atrium, LAHB: left anterior hemiblock, LBBB: left bundle branch block, LV: left ventricle, LVH: left ventricular hypertrophy, PA: pulmonary artery, RV: right ventricle.

Table 6: Recommendations for right heart catheterization in patients with pulmonary hypertension due to left heart disease (PH-LHD).

Recommendation	Class	Level
RHC is recommended in patients with congenital cardiac shunts to support decisions on surgical or interventional corrections.	I	C
RHC is recommended in patients with PH due to left heart disease or lung disease if organ transplantation is being considered.	I	C
When measurement of PAWP is unreliable, left heart catheterization should be considered to measure LVEDP.	IIa	C
RHC may be considered in patients with suspected PH and left heart disease or lung disease to assist in the differential diagnosis and to support treatment decisions.	IIb	C

LVEDP: left ventricular end-diastolic pressure, PAWP: pulmonary artery wedge pressure, PH: pulmonary hypertension, RHC: right heart catheterization.

Table 7: Characteristics used to differentiate "classical" pulmonary arterial hypertension (PAH) from "PAH with comorbidities"

Parameter	Characteristics
Hemodynamic characteristics	• PVR <3.5 WU • PAWP 12–15mmHg and PVR >3.5 but <6.0 WU
Risk factors for left heart disease[a]	• BMI≥30kg/m^2 • Arterial hypertension • Diabetes mellitus (any form) • Known significant CHD

BMI: body mass index, CHD: coronary heart disease, PAWP: pulmonary artery wedge pressure, PVR: pulmonary vascular resistance, WU: Wood units.

Table 8: Definitions and management of pulmonary hypertension due to chronic lung disease.

Underlying lung disease	mPAP<25mmHg	mPAP≥25 and <35mmHg and CI≥2.0L/min/m^2	mPAP≥35mmHg or mPAP≥25mmHg and CI<2.0L/min/m^2
• **COPD with FEV_1≥60% pred** • **IPF with FVC≥70% pred** • **No or only few bronchial or parenchymal changes on CT**	• No PH • PAH drugs not recommended	• PH classification unclear • Currently no data to support treatment with PAH drugs	• PH classification unclear: differentiate between PAH (Group 1) with concomitant lung disease or PH due to lung disease (Group 3)
• **COPD with FEV_1<60% pred** • **IPF with FVC<70% pred** • **On CT combined fibrosis and emphysema**	• No PH • PAH drugs not recommended	• PH-COPD, PH-IPF, PH-CPFE • Currently no data to support treatment with PAH drugs	• Severe PH-COPD, severe PH-IPF, severe PH-CPFE: Transfer to a centre with expertise in PH and lung disease for individualized decisions due to poor prognosis; randomized controlled studies are needed

CI: cardiac index, COPD: chronic obstructive pulmonary disease, CPFE: combined pulmonary fibrosis and emphysema, FEV1: forced expiratory volume in 1s, FVC: forced vital capacity, IPF: idiopathic pulmonary fibrosis, mPAP: mean pulmonary artery pressure, PAH: pulmonary arterial hypertension, PH: pulmonary hypertension, pred: predicted.

Table 9: Differential diagnosis Between Group 1 (PAH) and Group 3 (PH Due to Lung Disease) PH

Criteria Favoring Group 1 (PAH)	**Parameter**	**Criteria Favoring Group 3 (PH Due to Lung Disease)**
Normal or mildly impaired	Ventilatory function	Moderate to very severe impairment
FEV1 > 60% predicted (COPD)		FEV1 < 60% predicted (COPD)
FVC > 70% predicted (IPF)		FVC < 70% predicted (IPF)
Absence of or only modest airway or parenchymal abnormalities	High-resolution CT scan*	Characteristic airway and/or parenchymal abnormalities
Features of exhausted circulatory reserve		Features of exhausted ventilator reserve
Preserved breathing reserve		Reduced breathing reserve
Reduced oxygen pulse		Normal oxygen pulse
Low Co/Vo_2 slope		Normal Co/Vo_2 slope
Mixed venous oxygen saturation at lower limit		Mixed venous oxygen saturation above lower limit
No change or decrease in $PaCo_2$ during exercise		Increase in $PaCo_2$ during exercise

Features of exhausted circulatory reserve are also noted in severe PH-COPD and severe PH-IPF, but are then accompanied by major lung function and CT abnormalities.

C_O/V_{O_2} : cardiac output/oxygen consumption ratio;

COPD, CT: computed tomography;

DPLD: diffuse parenchymal lung disease;

FEV1: forced expiratory volume in 1 s;

FVC: forced vital capacity ;

IPF; PaC_{O_2} partial pressure of carbon dioxide in arterial; blood ;

PAH PH: pulmonary hypertension;

PVOD: pulmonary veno-occlusive disease.

Table 10

Recommendation	Class	Level
Optimization of the treatment for the underlying condition is recommended before considering assessment of PH-LHD (*i.e.* treating structural heart disease).	I	C
It is recommended that other causes of PH (*i.e.* COPD, SAS, PE, CTEPH) are identified and treated, where appropriate, before considering assessment of PH-LHD.	I	C
It is recommended that invasive assessments for PH are performed in patients on optimized volume status.	I	C
Patients with PH-LHD and a severe pre-capillary component, as indicated by a high DPG and/or high PVR, should be referred to an expert PH center for a complete diagnostic workup and an individualized decision regarding treatment.	IIa	C
The importance and role of vasoreactivity testing in PH-LHD is not established, except in patients who are candidates for heart transplantation and/or LVAD implantation.	III	C
The use of targeted PAH-approved therapies is not recommended in PH-LHD.	III	C

COPD: chronic obstructive pulmonary disease, CTEPH: chronic thromboembolic pulmonary hypertension, DPG: diastolic pressure gradient, LVAD: left ventricular assist device, PE: pulmonary embolism, PH: pulmonary hypertension, PH-LHD: pulmonary hypertension with left heart disease, PVR: pulmonary vascular resistance, SAS: sleep apnoea syndrome.

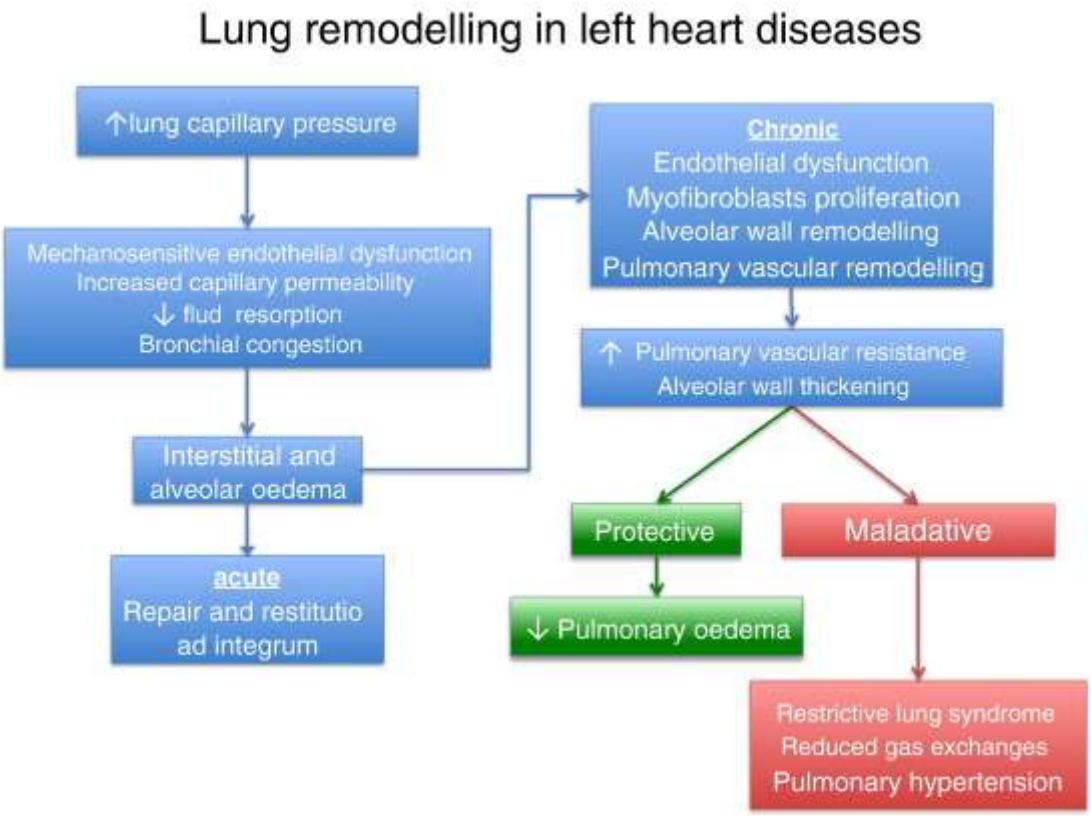

Figure 1: Pathophysiology of lung vascular and structural remodeling associated with LHD.

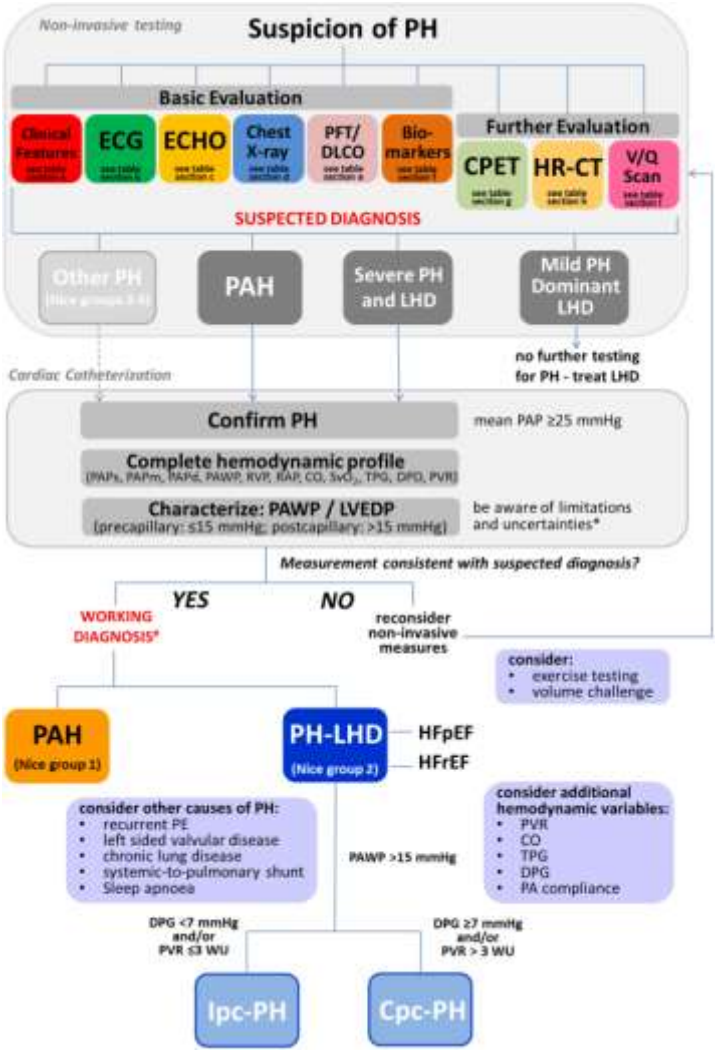

Fig. 2 Algorithm to differentiate between pulmonary arterial hypertension (PAH) and pulmonary hypertension with left heart disease (pH-LHD)