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PULMONARY HYPERTENSION IN CHILDREN AND ADOLESCENTS. A CHALLENGE

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ABSTRACT

Pulmonary Hypertension is not a disease but a hemodynamic condition, caused by various etiologies, which are different in children and adults, not only in terms of the age of onset but also as for incidence and prognosis. In the pediatric population a multifactorial etiology is typical. As this condition is rare and caused by different etiologies both a high clinical suspicion and a complete diagnostic algorithm are necessary for proper diagnosis and adequate staging to choose the best treatment option. In this manuscript, the definition, classification and recommendations of PH treatment in children will be presented, considering the updates based on results of studies and expert opinions exposed at the World Symposium of Pulmonary Hypertension (WSPH) that takes place every 5 years.

Key words: Hypertension, Pulmonary, Children, bronchopulmonary dysplasia

INTRODUCTION

Pulmonary circulation is characterized for being a low resistance and high capacitance system, prepared to receive large flux variations with minimal changes in pressure. The mean pulmonary arterial pressure (mPAP) at rest is 14mmHg +/- 3mmHg. This value is independent of race, sex and is slightly influenced by age. In regards to the behavior of pulmonary pressure in exercise, there is great variability according to age, sex and degree of physical training, so a definition of Pulmonary Hypertension (PH) with exercise is currently not established.

In 2013, PH was defined, according to the WSPH, as mPAP ≤ 25 mmHg, measured at rest and by right heart catheterization in patients older than 3 months of age, adding to this definition that PH due to congenital heart disease the Pulmonary Vascular Resistance Index (PVRI) is > 3 UW.m2.

In 2018, during the 6th World Symposium on Pulmonary Hypertension (6thWSPH) in Nice, a change in the definition is proposed, based on the fact that adding two standard deviations to the average value of 14mmHg gives an abnormal mPAP value, with the new value defining normal limit at 20mmHg (1).

Pulmonary Arterial Hypertension (precapillary) is considered, according to this last symposium of experts, to be mPAP > 20mmHg, Wedge Pressure (WP) ≤ 15mmHg and pulmonary vascular resistance ≥ 3 UW, using pediatric vascular resistance indexed per m2 of body surface (2). When the pulmonary vascular resistance is included in the definition, it should be noted that the rise of the mean pressure is due to pulmonary vascular disease and not to a hyperdynamic state.

Postcapillary Pulmonary Hypertension is defined at mPAP > 20mmHg with WP > 15mmHg and pulmonary vascular resistance < 3UW (Table 1) (2).

Table 1. Definition of pulmonary hypertension.
Based on the 6th World Symposium on Pulmonary Hypertension, Nice 2018 (6th WSPH Nice 2018)).

1) Pulmonary Arterial Hypertension (precapillary) Groups 1,3,4 and 5 of the classification PAPm > 20mmHg + PW ≤ 15mmHg y PVR ≥ 3UW
2) Isolated pulmonary postcapillary hypertension Group 2 and 5 PAPm > 20mmHg + PW > 15mmHg y PVR < 3UW
3) Combined pulmonary hypertension (precapillary + postcapillary) Group 2 and 5 PAPm > 20mmHg + PW > 15mmHg y PVR ≥ 3UW

In patients older than 3 months of age.
In pediatrics it is suggested to use pulmonary vascular resistance (PVR) indexed by body surface: IRVP ≥ 3UWxm2

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EPIDEMIOLOGY AND CLASSIFICATION

In a rare condition such as PH, patient records are essential to know the incidence, prevalence, sex difference, age at the time of presentation, the most frequent etiologies, their natural evolution without treatment and the response to same.

The main records in pediatric pulmonary hypertension (3,4,5) show us that the average age at the time of diagnosis of the disease is 7 years old, predominantly with females 59%, and is associated with chromosomal abnormalities in 13% mainly trisomy 21.

The estimated incidence of reported PH considering all categories of the classification is 4 to 10 cases per million children per year, with a prevalence of 20 to 40 cases per million in Europe (Spain, the Netherlands) and 5 to 8 cases per million children per year and 26 to 33 per million children in the United States (2).

The etiology in pediatrics differs from adults, there is a greater predominance of Idiopathic Pulmonary Arterial Hypertension (IPAH), PH associated with Congenital Heart Defect (CHD), and PH associated with lung development pathologies. Therefore, the most frequent etiologies in pediatrics are found in group 1 and group 3 of the classification. (table2) (2).

PH is classified into 5 groups according to their pathophysiology. This classification is the same as that used in adults, so some pediatric cases are difficult to fit into it. There is also a pediatric classification developed in the consensus of the Pulmonary Vascular Research Institute (PVRI) in 2011 which, although it is more complete for pediatric patients, unfortunately is not used (6). Currently the classification of the 6th World Symposium of Pulmonary Hypertension that was held in Nice in 2018 (6thWSPH) (table2) is used. Groups 1, 3, 4 and 5 present pathology of the precapillary pulmonary arteriole. In group 2 the cause is postcapillary pulmonary hypertension.

Group 1: Pulmonary Arterial Hypertension (PAH)

This group includes Idiopathic Pulmonary Arterial Hypertension (IPAH), whose incidence varies according to the different registries between 0.47 to 1.2 cases per million

Table 2. Updated classification of pulmonary hypertension. The changes made at the 6th World Symposium of Pulmonary Hypertension Nice 2018, of the classification are indicated in red (6th WSPH NICE 2018).

1. Pulmonary Arterial Hypertension
- 1.1. Idiopathic
- 1.2. Heritable
- 1.3. Induced by drugs and toxins
- 1.4. Associated with:
- 1.4.1. Connective tissue diseases
- 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 of Ca Blockers
- 1.6 PAH related to pulmonary venous or capillary disease (PVOD / PCH)
- 1.7 Persistent PH syndrome of the newborn

2. Pulmonary hypertension due to left heart disease
- 2.1. PH due to heart failure with decreased LV ejection fraction
- 2.2. PH due to heart failure with conserved LV ejection fraction
- 2.3. Cardiac valvular pathology
- 2.4. Congenital or acquired conditions of PH pulmonary postcapillary (pulmonary vein stenosis, Cor Triatriatun, obstructive TAPVR, mitral or aortic stenosis, Ao coarctation)

3. Pulmonary hypertension due to Pulmonary disease and / or hypoxemia
- 3.1. Obstructive pulmonary disease
- 3.2. Restrictive Pulmonary Disease
- 3.3. Other lung diseases with mixed restrictive and obstructive pattern
- 3.4. Hypoxia without lung disease
- 3.5. Pulmonary development disorders (BPD, diaphragmatic hernia, DownS, alveolocapillary dysplasia, etc.)

4. Pulmonary hypertension due to arterial obstructions
- 4.1 Chronic thromboembolic PH
- 4.2 Other arterial obstructions (tumor, disease-free arteritis Connective Tissue, parasitosis, congenital PA stenosis)

5. Pulmonary hypertension with unclear or multifactorial mechanisms
- 5.1. Hematological Disorders
- 5.2. Systemic and metabolic disorders: Histiocytosis, neurofibromatosis, Gaucher, GSD, sarcoidosis
- 5.3 Other (chronic kidney disease with or without dialysis, mediastinal fibrosis)
- 5.4. Complex congenital heart disease (segmental PH, single operated and non-operated ventricle, scimitar syndrome)

children per year, with a prevalence rate of 2.1 to 4.4 cases per million children. With (IPAH) the diagnosis is by exclusion of the different etiologies.

In Group1, Heritable PAH (HPAH) the main genes involved being BMPR2, ACVRL1, as in adults and some more frequent in pediatrics such as TBX4 and SOX 17, variants of the latter associated with PH in congenital heart disease (7 and 8) are also found.

Also belonging to this group:

* PH induced by drugs and toxins

* PH associated with:

a) Connective tissue diseases: rare in pediatrics but which should be suspected in the face of rapid deterioration of the patient.

b) HIV: very rare except in endemic areas.

c) Portal hypertension: uncommon, about 2% according to different records, although it is important to rule it out in patients with liver disease that may be included in the liver transplant list since if present it may contraindicate it.

d) Congenital heart defect includes four subcategories: Eisenmenger syndrome; congenital heart defect with left to right shunts operable and not operable; hypertension associated with small defects; and that associated with operated congenital heart defect. It does not include patients with univentricular physiology or segmental PH who, since 6thWSPH, were placed in Group 5.

e) Schistosomiasis: uncommon in developed countries and without studies about specific therapy in pediatrics.

* Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis, rare in pediatrics.

* Persistent newborn PH (PNPH): It is the most frequent cause of transient PH (30.1 cases per million) and continues to increase given the greater survival of extreme premature children and their best treatment. The presence of PNPH is inversely proportional to gestational age. The 6thWSPH pediatric working group considers this condition as a syndrome with multiple conditions associated with prenatal (chorioamnionitis, preeclampsia, etc.) and perinatal events, such as Meconium Aspiration Syndrome, sepsis, pneumonia, asphyxiation, among other causes which can alter lung development and perhaps increase the risk of subsequent development of PAH during life (2). When PNPH does not resolve within 2 weeks, other causes included in Group 3 of the classification, such as alterations of the pulmonary parenchyma or Alveolar Capillary Dysplasia should be evaluated.

A new category was added to Group1 in Nice 2018, it was the long-term PAH responding to calcium channel blockers. The pulmonary vasoreactivity test is used to define this subgroup based on the Sitbon criteria (2). These patients have a different behavior from idiopathic patients, with a better prognosis than IPAH. Between 8-15% of children with IPAH would correspond to this group.

Group 2: PH associated with left heart disease

This group includes all congenital postcapillary obstructive lesions (mitral stenosis, aortic, and pulmonary vein stenosis, coarctation of the aorta, cor triatriatum, total anomalous pulmonary venous return) and left ventricular dysfunction.

Group3: PH due to lung disease and / or hypoxia

This group has grown in recent years and currently the etiologies it includes are highly frequent in pediatrics. At the 6thWSPH, to this group was added the category of pulmonary development disorders that includes Bronchopulmonary Dysplasia (BPD), congenital diaphragmatic hernia, Down Syndrome, Alveolar Capillary Dysplasia with misalignment of pulmonary veins, pulmonary hypoplasia and disorders surfactant proteins, among others.

BPD is one of the causes that has increased the most due to the better survival of premature infants, presenting in 25-38% of cases, of which 25% will have PH, a mortality of 47% two years after diagnosis (9).

PH is present in the majority of cases of congenital diaphragmatic hernia, being its multifactorial cause, including pulmonary hypoplasia, as well as abnormal pulmonary vasoreactivity and alterations in the size and function of the left ventricle that lead to changes in pressure and pulmonary flow.

Group 4: PH due to arterial obstructions

Includes chronic thromboembolic disease, rare in pediatrics and other pulmonary artery obstructions, among them due to tumors, arteritis, parasitic diseases (hydatidosis for example) and those that may be associated with heart disease, either congenital or post-surgical pulmonary artery stenosis.

Group 5: PH due to unclear or multifactor mechanisms

This group includes hematologic disorders, systemic and metabolic disorders such as Histiocytosis, Gaucher disease, glycogenosis, complex congenital heart disease with univentricular physiology, segmental pulmonary hypertension and scimitar syndrome.

Thyroid diseases and splecnectomy were excluded as causes of PH in the last WSPH.

Patients with univentricular physiology make up a very heterogeneous group of severe congenital heart diseases, which can develop early or in their late evolution, pulmonary vascular disease that leads to rapid deterioration of their hemodynamic condition and in extreme cases contraindicates the possibility of performing elective surgery for them, such as the Total Bypass of the Subpulmonary Ventricular or Fontan-Kreutzer procedure. The mechanisms that produce the development of pulmonary vascular disease in these patients are being studied, which is why they are currently included in group 5.

DIAGNOSIS

The diagnosis of PH is based on clinical suspicion and a good interrogation of personal and family history since symptoms at first are nonspecific (10,11).

Since pediatric PH is multifactorial and of very different etiologies, a thorough diagnostic algorithm must be performed, looking first, obviously, for the most frequent causes in pediatric age (table 3).

Faced with symptoms that suggest PH such as dyspnea on exertion, angina, presyncope and syncope, the latter more frequent in pediatrics than in adults, family history of PH, associated genetic syndromes or physical examination compatible with PH - characteristically the second noise increased -, an electrocardiogram (ECG), chest radiograph and color Doppler Echocardiography will be requested.

The ECG has a sensitivity of 55% and specificity of 70% for diagnosis, with the most frequent findings being a deviation of the QRS axis to the right and signs of overloading of right cavities. The presence of arrhythmias and repolarization abnormalities in precordial leads suggest severity. Given the low sensitivity, a normal ECG does not exclude PH (12).

Chest X-ray is abnormal in 90% of patients with PH, the most frequent findings being cardiomegaly at the expense of right cavities and dilatation of the pulmonary artery trunk.

The Echocardiogram is the non-invasive method of choice for the detection of PH, since it allows quantification, approximation to the etiological diagnosis, to estimate its severity, assess the impact on the right ventricle, detect prognostic factors and monitor the patient (13).

The exception is patients with Bronchopulmonary Dysplasia (BPD), in which the echocardiogram adequately estimates the presence of PH at 80%, but only correctly estimates its severity at 47%, according to a study by Mourani of echocardiography compared to cardiac catheterization (14.) In these patients, due to the vasoreactivity they present in situations such as infections, the results of the echocardiogram may overestimate the baseline PH, therefore it is recommended to perform the echocardiogram once the infectious intercurrences are resolved.

The echocardiogram will define if a patient has high, intermediate or low probability of presenting PH according to the value of tricuspid regurgitation and the presence of the so-called indirect signs of PH (15) (table 4).

Table 3. Diagnostic algorithm of pulmonary hypertension. 6thWSPH (the 6th World Symposium on Pulmonary Hypertension,) Nice 2018. CHD: Congenital Heart Disease, CH: clinical history, CTD: Connective Tissue diseases, IPAH: Idiopathic pulmonary arterial hypertension, HPAH Hereditary Pulmonary Arterial Hypertension, VOPD: venoclusive pulmonary disease.

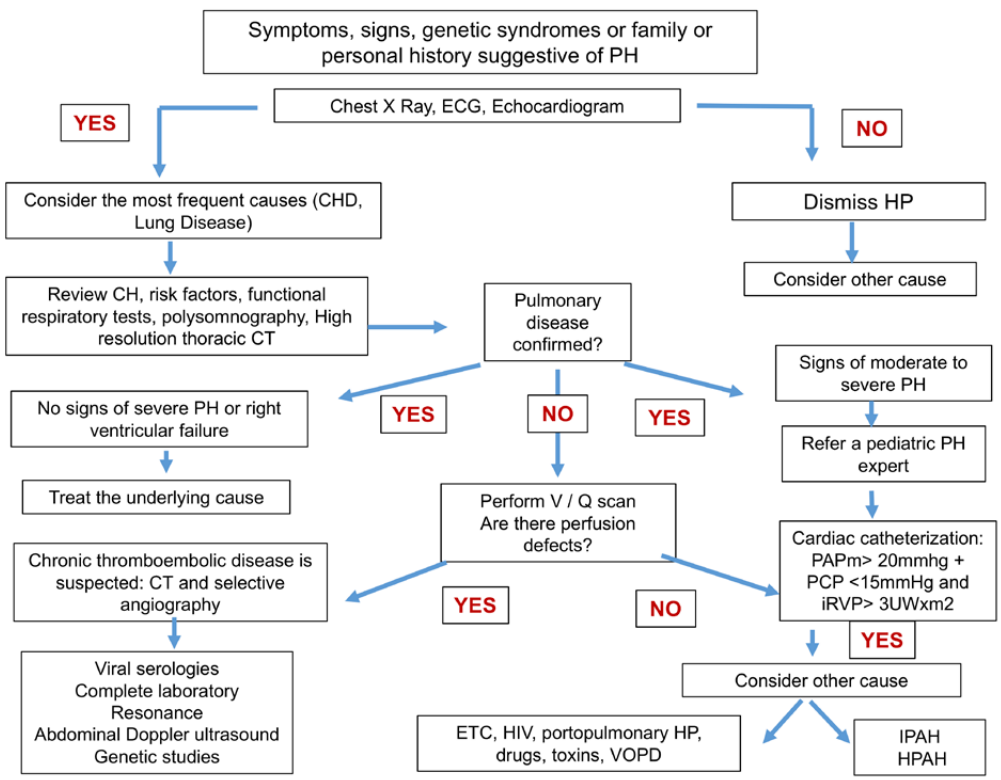


Table 4. Categorization of PH (Pulmonary Hypertension) by Echocardiogram: probability of PH according to the value of tricuspid regurgitation and the presence of indirect signs of PH.

Tricuspid insufficiency	Presence of PH signs	PH probability
< 2,8m/s or not measurable	NO	Low
< 2,8m/s not measurable	YES	Intermediate
2,9-3,4 m/s	NO	Intermediate
2,9-3,4 m/s	YES	High
> 3,4m/s	Not necessary	High

Once the suspicion of PH is confirmed by echocardiography, the most frequent causes are ruled out: congenital heart disease and lung disease, the latter through functional respiratory tests, polysomnography and high-resolution chest computed tomography (HRCT). Simultaneously, laboratory studies are requested according to personal, family history and physical examination, such as viral serology, collagenogram, abdominal echo Doppler, resonance and angiotomography due to the probability of thromboembolic disease.

Finally, cardiac catheterization is considered the "gold standard" for diagnosis of PH, but its performance should be evaluated according to the risks involved for the pediatric patient. Between 1-3% has reported risks of serious complications, associated with younger age and worse clinical condition. The risk of mortality (0.5 to 1%) and complications is much higher than in adults (2). In the TOPP registry (3), 7% of serious complications are reported within 24 hours of catheterization, so it is suggested that patients remain hospitalized during that period. Cardiac catheterization should be performed in specialized centers with experience in the treatment of patients with PH and it is recommended that it be done right and left to rule out any heart disease that has not been diagnosed on the echocardiogram. It allows to confirm the diagnosis of PH, assessing the severity of hemodynamic impact, evaluating prognosis, deciding treatment and providing variables that help categorize the patient. In patients with IPAH, HPAH and congenital heart disease, the pulmonary vasoreactivity test is indicated, nitric oxide being the drug of choice (20-80ppm for 10 minutes). IPAH / HPAH allows to define if they qualify for high-dose calcium channel blocker (CCB) therapy which implies a better prognosis. In congenital heart disease, the pulmonary vasoreactivity test is performed to evaluate surgical or endovascular therapeutic possibilities. Regarding vasoreactivity test, the 6thWSPH recommends the use of the Sitbon criteria: it is considered positive if it presents a reduction in mPAP ≥ 10mmHg and reaches an absolute value of mPAP ≤ 40mmHg with an increased or unchanged cardiac output.

In patients in functional class IV, specific stabilization and vasodilator treatment is performed under strict control in intensive care, and then if the patient is in conditions the catheterization would be performed.

CATEGORIZATION

While performing the diagnostic algorithm to confirm PH and find the etiology of the same, the patient must be categorized. That is, assess whether they are high or low risk. Categorization is essential to decide the therapeutic scheme and evaluate the progression of the disease at the following checkups (Table5).

TREATMENT

The goal of treatment is to provide the patient with the best possible quality of life waiting for more and better therapies, and greater options for a bi-pulmonary transplant. The expectation and quality of life of patients with PH has improved in recent decades thanks to advances in the development of specific vasodilator therapies. Until now, PH was considered "incurable" and only reversible in some cases, such as in congenital heart disease or PPH in the newborn (13,14,16,17).

General treatment consists of pharmacological measures for the treatment of heart failure, achieving adequate nutrition and avoiding risk situations for the patient:

- Administration of oxygen if saturation is less than

Table 5. Categorization of the patient with pulmonary hypertension IPAH / HPAH. 6thWSPH (the 6th World Symposium on Pulmonary Hypertension,) Nice 2018.
RV: right ventricle; BNP: natriuretic peptide; NTproBNP: NT terminal portion of the natriuretic pro peptide, RA: right atrium; LV: left ventricle; TAPSE: Tricuspid annular plane systolic excursion; FAC: fraction of area of change of RV; CI: cardiac index; RAP: right atrial pressure; PVRI: pulmonary vascular resistance index; PACI: pulmonary arterial complience index.

LOW RISK	DETERMINANT	HIGH RISK
No	Clinical evidence of RV failure	Yes
No	Symptom Progression	Yes
>350 mts	March Test (≥ 7 years or ocording development)	≤ 350 mts
Normal	Growth	Delay weight/height
I-II	Functional Class	IV
Minimally high	BNP / NTproBNP	Significantly high, rising
	Echocardiogram	Enlargement RA / RV LV size decrease Increase in the ratio RV / LV TAPSE decreased Low RV FAC Pericardial effusion
Systemic IC > 3 l / min / m2 Systemic venous sat > 65% Vasoactivity test +	Hemodynamic findings	Systemic IC < 2.5 l / min / m2 Systemic venous sat < 60% RAP > 10 mmHg PVRI > 20 UW m2 PACI < 0.85

92% or clinical improvement is demonstrated.

- Administration of diuretics: furosemide and spironolactone, and in the case of patients with BPD hydrochlorothiazide and spironolactone, the latter has showed effect in neonates and children on the remodeling of the right ventricle.
- Digoxin administration: Used in case of right ventricular failure but there is no clear evidence of its usefulness in pediatrics.
- Influenza and pneumococcal vaccination (respiratory infections have high mortality in patients with PH)
- Avoid trips at height and by plane. And if necessary use supplemental oxygen.
- Perform physical activity according to the functional class of the patient, avoiding isometric exercise.
- Adequate nutritional control
- Prevent pregnancy

Regarding specific vasodilator drugs currently available for the treatment of PH, we can divide them according to their route of action into:

1) Calcium channel blockers: nifedipine, diltiazen.
2) Nitric oxide pathway: nitric oxide, sildenafil, tadalafil, riociguat.
3) Prostanoids stimulating cAMP: iloprost, treprostinil, epoprostenol.
4) Selective IP receptor agonist: selexipag.
5) Endothelin receptor antagonists: bosentan, ambrisentan, macitentan

The algorithm described in Table 6 is used to decide the therapeutic scheme, classifying the patient according to the pulmonary vasoreactivity test. Those who are positive, older than one year, with good ventricular function, without Eisenmenger, can receive treatment with calcium blockers: nifedipine 2-5 mg / kg / day divided into 3 daily doses or

diltiazen 3-5 mg / kg / day. The rest will receive specific vasodilator treatment as they have been categorized in low-risk or high-risk patients (Table 6).

In the case of patients with BPD, the algorithm proposed by the Pediatric Pulmonary Vascular Disease Network is the one presented in table 7.

Surgical treatment is indicated in extreme situations in which it is impossible to control the symptoms of heart failure, recurrent syncopes and when vasodilator treatment does not obtain results, having resorted to all the specific drugs available. They are high-risk procedures and consist in achieving, through the creation of a shunt, the decompression of the right ventricle, improving cardiac output.

a) Potts anastomosis: creation of a shunt between descending aorta and left pulmonary branch in patients with suprasystemic pressure. Unsaturation occurs only in the lower part of the body with normal saturation in coronaries and brain.

b) Atrial septostomy: creation of a shunt at the atrial level in patients with recurrent, severe syncopes and low minute volume. Contraindicated in patients with saturation less than 90% and if the pressure in AD is greater than 20mmHg.

Lung transplantation is the last option, indicated only for patients in functional class IV in which other treatments have failed and whose life expectancy without a transplant is short (less than 1-2 years). Bi-pulmonary transplantation is indicated to show better results than uni-pulmonary and cardiopulmonary. Mortality is high and the long-term results in pediatrics are not good, with a 5-year mortality of 50% and a 10-year mortality of 80%.

CONCLUSIONS

PH is a rare, chronic condition with multiple etiologies, various forms of clinical presentation and reserved prognosis. However, a successful clinical evaluation, the application of the corresponding diagnostic algorithms, interpreted by highly

Table 6. IPAH / HPAH Treatment Algorithm. 6thWSPH (the 6th World Symposium on Pulmonary Hypertension,) Nice 2018
PDE-5i: 5 phosphodiesterase inhibitors (Sildenafil, Tadalafil); ERA: Endothelin receptor antagonists, IV: intravenous ; SC: subcutaneous.

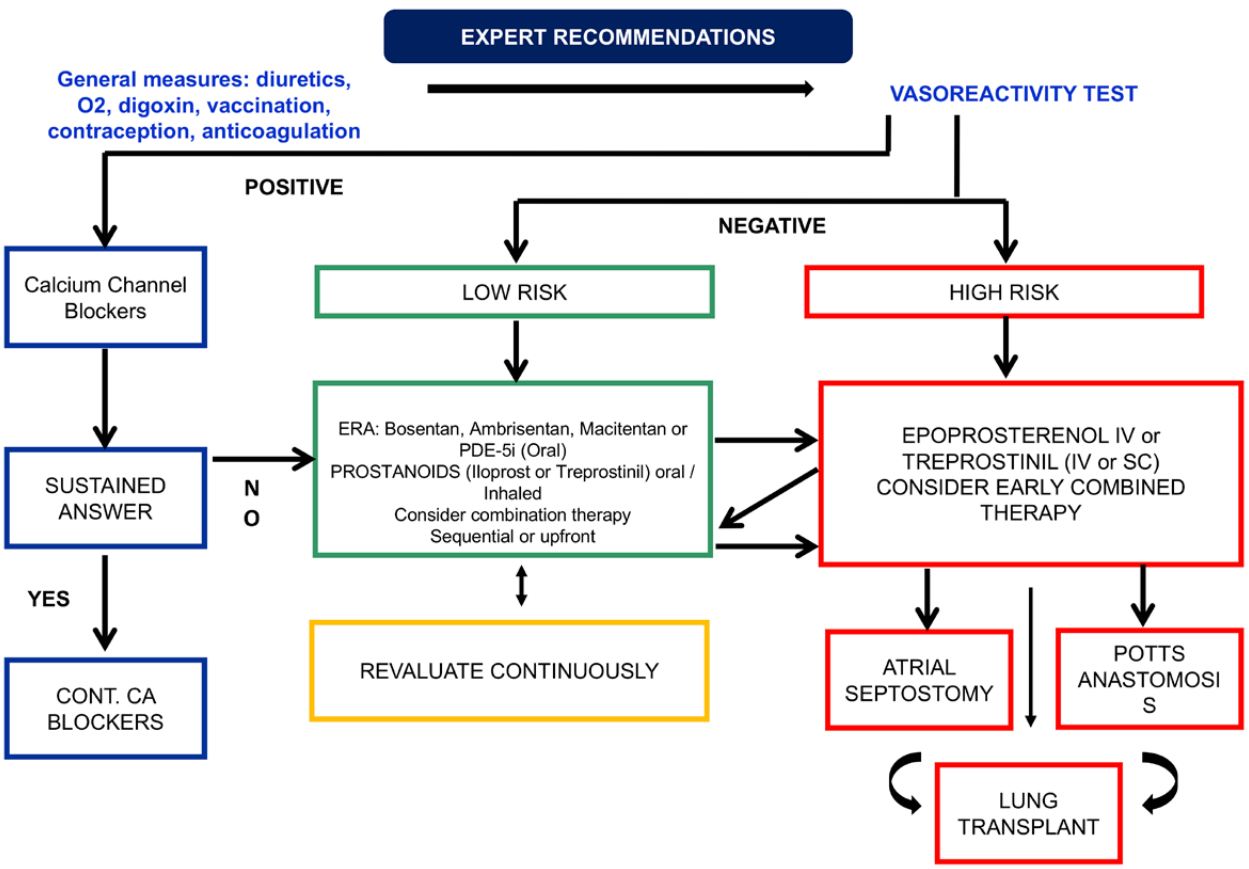
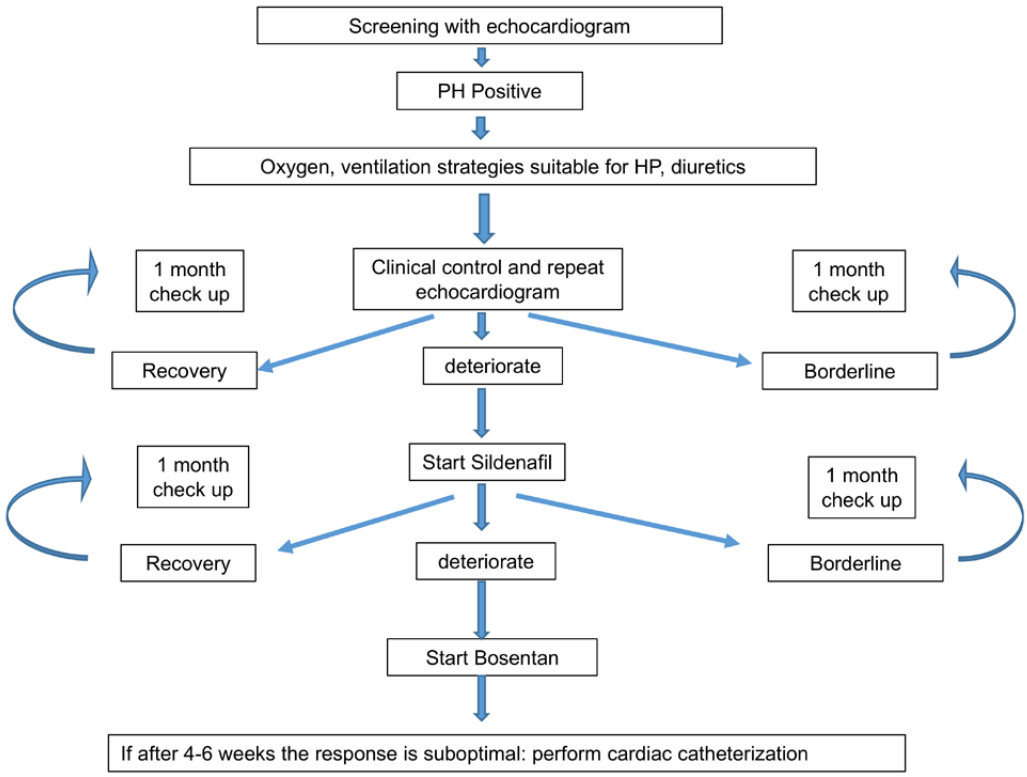


Table 7. Algorithm Patient Management with BPD.



specialized health teams, pharmacological research with increasingly specific drugs, acting on various etiopathogenetic mechanisms, have undoubtedly made it possible to improve quality and expectation of patients' lives.

Working with a multidisciplinary team for the best approach for these patients is a challenge and a necessity.

I have no conflicts of interest

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