The Right Heart and Pulmonary Circulation (III)

# The Pulmonary Circulation in Heart Failure

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Pulmonary hypertension due to left heart disease is a pathophysiological and hemodynamic state which is present in a wide range of clinical conditions that affect left heart structures.

Although the pulmonary circulation has traditionally received little attention, it is reasonable to say that today it is a fundamental part of cardiological evaluation. In patients with heart failure, the most important clinical factors are the presence of pulmonary hypertension and right ventricular function. These factors are also essential for determining prognosis and must be taken into account when making some of the most important therapeutic decisions.

The pathophysiological process starts passively but later transforms into a reactive process. This latter process, in turn, has one component that can be reversed with vasodilators and another component that is fixed, in which the underlying mechanism is congestive vasculopathy (ie, essentially medial hypertrophy and pulmonary arterial intimal fibrosis).

Currently no specific therapy is available for this type of pulmonary hypertension and treatment is the same as for heart failure itself. The drugs that have been shown to be effective in pulmonary arterial hypertension have generally had a neutral effect in clinical trials. Nevertheless, we are involved in the clinical development of a number of groups of pharmacological compounds that will enable us to make progress in the near future.

**Key words:** *Heart failure. Pulmonary hypertension. Vasodilators. Heart transplant.*

## La circulación pulmonar en la insuficiencia cardiaca

La hipertensión pulmonar asociada a cardiopatía izquierda es una entidad fisiopatológica y hemodinámica presente en una amplia variedad de situaciones clínicas que afectan a las estructuras cardiacas izquierdas.

Aunque tradicionalmente la circulación pulmonar ha recibido escasa atención, a día de hoy podemos afirmar que es un elemento de primer orden en la evaluación cardiológica. En el paciente con insuficiencia cardiaca, la presencia de hipertensión pulmonar y la función del ventrículo derecho son factores determinantes del cuadro clínico, elementos esenciales en la valoración pronóstica y variables indispensables para algunas de las más importantes decisiones terapéuticas.

El proceso fisiopatológico se inicia de forma pasiva para luego dar paso a un componente reactivo. Éste, a su vez, tiene un componente reversible con vasodilatadores y otro fijo, cuyo sustrato es la vasculopatía congestiva (esencialmente hipertrofia de media y fibrosis de la íntima arterial pulmonar).

No existe tratamiento específico para este tipo de hipertensión pulmonar y su tratamiento es el de la propia insuficiencia cardiaca. Los fármacos que se han mostrado eficaces en el tratamiento de la hipertensión arterial pulmonar han tenido generalmente un resultado neutro en los estudios clínicos. Sin embargo, asistimos al desarrollo clínico de algunos grupos farmacológicos que nos permitirán avanzar en un futuro próximo.

**Palabras clave:** *Insuficiencia cardiaca. Hipertensión pulmonar. Vasodilatadores. Trasplante cardiaco. Vasodilators. Heart transplant.*

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## INTRODUCTION

The right ventricle and pulmonary circulation have traditionally been considered to play very much a secondary role in cardiology in general and heart failure in particular.[1]

However, currently, we can affirm that both right ventricular (RV) function and pulmonary circulation status are of utmost importance in cardiology. Specifically, in patients with heart failure, pulmonary hypertension (PH) and RV function are determining factors in the clinical picture, and essential prognostic

ABBREVIATIONS

mPAP: mean pulmonary artery pressure
PAH: Pulmonary arterial hypertension
PH: pulmonary hypertension
PWP: pulmonary wedge pressure
RV: right ventricular
TPG: transpulmonary gradient

**TABLE 1. Current Classification of Pulmonary Hypertension (Dana Point,[4] 2008)**

1. Pulmonary artery hypertension
  1.1. Idiopathic
  1.2. Hereditary
    1.2.1. BMPR2
    1.2.2. ALK-1, endoglin (with or without hereditary telangiectasia)
    1.2.3. Unknown
  1.3. Drug- and toxin-induced
  1.4. Associated pulmonary arterial hypertension
    1.4.1. Connective tissue disorders
    1.4.2. HIV infection
    1.4.3. Portal hypertension
    1.4.4. Congenital heart disease
    1.4.5. Schistosomiasis
    1.4.6. Chronic hemolytic anemia
  1.5. Persistent newborn pulmonary hypertension
1'. Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension caused by left heart disease
  2.1. Systolic dysfunction
  2.2. Diastolic dysfunction
  2.3. Valve disease
3. Pulmonary hypertension secondary to pulmonary diseases and/or hypoxemia
  3.1. Chronic obstructive pulmonary disease
  3.2. Interstitial pulmonary disease
  3.3. Other pulmonary diseases with mixed restrictive and obstructive patterns.
  3.4. Sleep-disordered breathing
  3.5. Alveolar hypoventilation disorders
  3.6. Chronic high-altitude exposure
  3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. Pulmonary hypertension with unclear or multifactorial mechanisms
  5.1. Hematological disorders: myeloproliferative, splenectomy
  5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
  5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
  5.4. Others: tumoral obstruction, fibrous mediastinitis, chronic renal failure with dialysis

variables and indispensable for some of the most important therapeutic decisions.

It is estimated that approximately 60% of patients with severe left ventricular systolic dysfunction and 70% of those with isolated diastolic dysfunction experience PH.[2] Given the high prevalence of these conditions, we can affirm that PH secondary to left heart disease, and specifically to heart failure, is one of the most common types of PH.

## DEFINITIONS

The new clinical practice guidelines for the diagnosis and treatment of pulmonary hypertension define PH secondary to left heart disease as a pathophysiological and hemodynamic entity that may present as any one of a wide variety of clinical entities that affect the left heart chambers and structures.[3]

PH secondary to left heart disease represents group 2 of the new modified Dana Point classification (Table 1).[4] It is one of the main representatives of the so-called non-PAH.[5]

The definition of PH secondary to left heart disease is coupled with the need for a hemodynamic study to confirm that the mean pulmonary artery pressure (mPAP) is ≥25 mm Hg at rest and that the pulmonary wedge pressure (PWP) is >15 mm Hg.

The 25 mm Hg cut-off has probably been chosen to make the hemodynamic limit more uniform for all forms of PH and because it is the value used in clinical trials and PH registries. However, the recent reassessment of the hemodynamic data available for healthy subjects has shown that normal mPAP at rest is 14 (3) mm Hg, with a maximum limit of normal rarely in excess of 20 mm Hg.[6] In fact, previously accepted definitions set the upper limit of normal for mPAP at 19 mm Hg.[7] Therefore, the significance of mPAP lying between 20 and 24 mm Hg is not clear and patients with a mPAP in this range need to be assessed further in epidemiological studies.[3]

## PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION IN HEART FAILURE

The lung, in addition to oxygenating venous blood, has the unique characteristic of being the only organ that spends the entire cardiac cycle at "low pressure," even when exercise causes up to a 5-fold increase in cardiac output. This is possible thanks to the enormous reserve of the pulmonary vascular bed. This capacity also contributes to the regulation of left ventricular filling by maintaining the transpulmonary gradient (TPG) (TPG=mPAP-PWP) within normal values, close to 5-7 mm Hg.
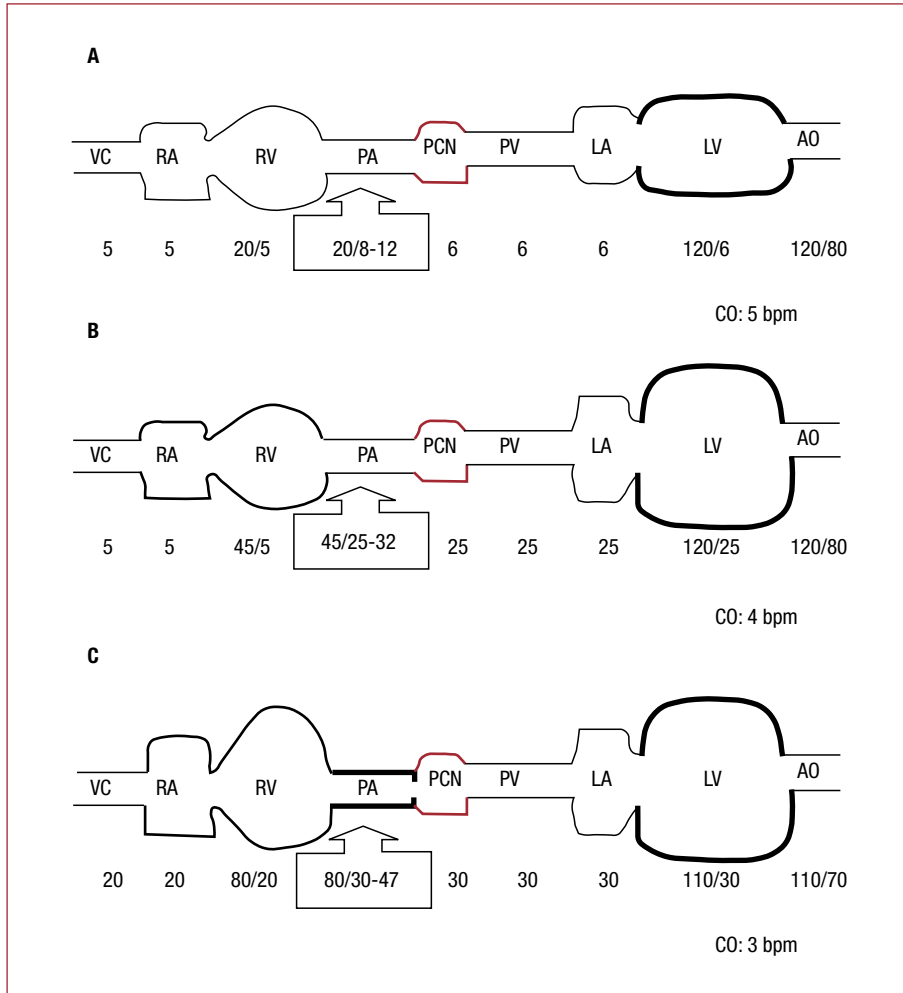
**Figure 1.** Schematic diagram of pulmonary circulation. A: healthy individual. B: heart failure and mild "passive" pulmonary hypertension. C: advanced heart failure and severe "reactive" pulmonary hypertension. The pressures (mm Hg) are presented from the vena cava (VC), right atrium (RA), right ventricle (RV), pulmonary artery (PA), pulmonary capillary bed (PCB), pulmonary vein (PV), left atrium (LA), left ventricle (LV), and the aorta (AO). CO indicates cardiac output in each case.

## Passive and Reactive Pulmonary Hypertension

PH in patients with heart failure may have passive or reactive PH (and in the latter case, reversible or irreversible), although in clinical practice it is usually mixed, that is, passive with a reactive component (Figure 1).

When elevated PWP occurs in patients with systolic, diastolic, or mixed heart failure (Table 2), there is initially a "passive" increase in mPAP in order to maintain normal TPG sufficient to facilitate flow from pulmonary circulation to the left side of the heart.

However, chronically elevated PWP is accompanied by a "reactive" increase in mPAP, in addition to the passive component, and so TPG increases. Clinical practice guidelines for PH introduce an additional hemodynamic definition to this entity[3]: Passive PH when TPG is ≤12 mm Hg and reactive or disproportionate PH when TPG is >12 mm Hg.

**TABLE 2. Classification of Pulmonary Hypertension Secondary to Left Heart Disease**

Left ventricular systolic dysfunction
    Dilated idiopathic cardiomyopathy
    Dilated ischemic cardiomyopathy
Left ventricular diastolic dysfunction
    Arterial hypertension
    Aortic stenosis
    Coronary artery disease
    Constrictive pericarditis
    Hypertrophic cardiomyopathy
    Restrictive cardiomyopathy
Mitral valve disease
    Mitral stenosis
    Mitral regurgitation
*Cor triatriatum*
Myxoma or left atrial thrombus

The reactive component, in turn, has a dynamic or functional component resulting from vasoconstrictive stimuli and a fixed component. The first is generally

reversible with vasodilator administration. However, the fixed component reflects remodeling of the pulmonary artery muscle, essentially in the form of medial hypertrophy and, to a lesser extent, intimal fibrosis. Thus, the pulmonary artery vessel partially loses its vasodilatory capacity. Depending on the extent of this loss, reactive PH will be more or less reversible (or fixed) when vasodilator drugs are administered.

Reactive PH eventually leads to RV dysfunction (as pulmonary pressure is the main determinant of afterload) and, finally, decreased cardiac output and right heart failure.

### Right Ventricle

The RV, in the context of heart failure, may be affected principally by the primary heart disease (idiopathic or ischemic cardiomyopathy) and/or by increased afterload leading to PH and its progression. As the RV becomes dilated in response to poorly tolerated pressure overload, restrictions imposed by the pericardium and the muscle fibers common to both ventricles (interventricular interdependence relationship) limit further RV dilation. This leads to a steeper gradient of the RV diastolic pressure-volume curve, such that a larger increase in RV pressure does not correspond to greater stretching of its free wall. At the same time, displacement of the ventricular septum reduces the left ventricular ejection fraction. Together, these 2 events lead to a net decrease in cardiac output. Once the cardiac output begins to decrease, ventricular failure progresses rapidly. After the decrease in cardiac load comes systemic hypotension; this reduces the RV perfusion pressure and favors ischemia of the free wall. RV ischemia further reduces contractile function, with still larger decreases in cardiac load, and a rapid downward spiral is initiated resulting in hemodynamic collapse.[8]

### Protection Against Pulmonary Edema

The development of fixed PH is one of the protective mechanisms against pulmonary edema in presence of chronically elevated left ventricular preload. Three basic mechanisms are known for protection against pulmonary edema in heart failure: increased interstitial lymphatic drainage, intralobular interstitial thickening, and pulmonary vascular remodeling.

In accordance with these mechanisms, PH leads to a significant reduction in RV output.[9] This in turn decreases the blood supply to the pulmonary capillary bed and protects against edema, in addition to subtly changing the clinical course of the patient: clinical manifestations of pulmonary congestion are reduced to be progressively replaced with systemic congestion.

In PH due to heart failure, 2 pathophysiological aspects should be analyzed: the factors that contribute to elevated pulmonary venous pressure and what takes place in the pulmonary vessel for PH to convert from the passive to reactive form.

### Factors that Contribute to Elevating Pulmonary Venous Pressure and Maintaining it Elevated

Most patients with chronic heart failure experience some degree of PH. However, although many aspects of this association are not known, it is known that greater severity and duration of heart disease is associated with more severe PH.

The factors that essentially contribute to maintaining chronically high pulmonary venous pressure are left ventricular diastolic dysfunction, mitral valve disease, and left atrial function and remodeling.

In presence of left ventricular dysfunction and dilation, systolic dysfunction undoubtedly contributes to elevated pulmonary venous pressure. However, greater severity of diastolic dysfunction and mitral regurgitation are more closely related to the development and severity of PH.[10]

In presence of mitral valve disease, the functional area of stenosis and size of the regurgitating orifice when the valve is incompetent are related to the degree of venous hypertension. However, the regurgitating or affected orifices are not closely related to the severity of PH and other factors, such as atrioventricular compliance, intervene in the development of PH.[11]

The left ventricle also actively participates in the pathophysiology of PH.[12] As has been shown in a canine model of heart failure, the increase in left-ventricular end-diastolic pressure leads to structural changes in the atrial wall: hypertrophy of the myocytes and increase in collagen matrix. A positive correlation has been found between markers of increased atrial collagen synthesis (greater atrial rigidity) and mPAP.[13] This atrial remodeling affects atrial systolic function, but above all, atrial compliance. The greater left atrial rigidity is transmitted in a retrograde direction without damping the high left-ventricular end-diastolic pressure.[14]

Despite all these aforementioned factors, there is great variability in the severity of PH associated with heart failure. Although the mechanisms implicated in this response variable are not known, it could be that genetic factors play a role. In fact, severe elevations in pulmonary artery pressure (systolic pressure ≥80 mm Hg) only occur in less than one-third of patients with chronic elevation of pulmonary venous pressure.
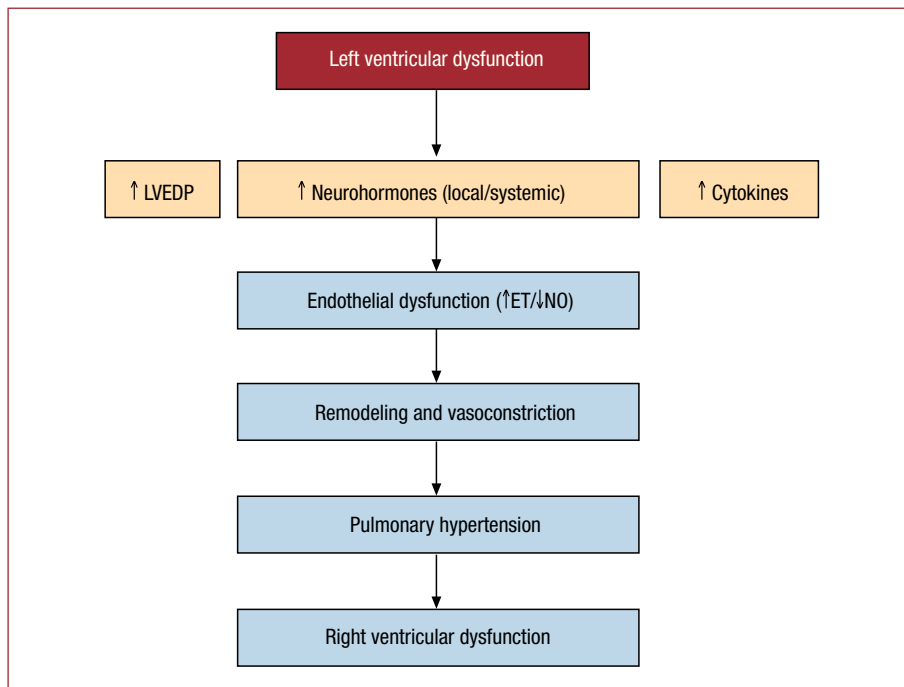
**Figure 2.** Possible relationship between presence of left ventricular dysfunction and secondary events that may lead to pulmonary arterial hypertension. ET indicates endothelin; NO, nitric oxide; ed-LVEDP, left ventricular and diastolic pressure.

## Factors That Contribute to Passive Pulmonary Hypertension Becoming Active Pulmonary Hypertension

While the initial idiopathic pulmonary artery hypertension (PAH) produces vascular damage of unknown cause, thereby inducing secondary remodeling and finally PAH, the opposite occurs in PH secondary to heart failure: the initial trigger is passive hypertension, which initiates the vascular remodeling process, probably by endothelial damage, eventually leading to severe and fixed PH (Figure 2).

PH associated with chronic heart failure of systolic origin is the most extensively studied at a molecular level. It seems that hemodynamic stress caused by the passive component of PH, the neurohormonal activation inherent in heart failure, and local and systemic production of cytokines trigger endothelial damage that initiates remodeling in the pulmonary artery vessel.

Nitric oxide (NO) generated in the endothelial cell of the pulmonary vascular bed acts on smooth muscle cells causing them to relax, inhibits their proliferation and hypertrophy and, by means of a joint action with prostacyclin, inhibits platelet aggregation and adhesion.

Some experimental models and clinical studies of heart failure point to deficient basal NO production and suggest that the resulting loss of NO-dependent vasodilation may contribute the development of PH.[15,16]

The endothelium (ET) is a vasoactive peptide also produced by endothelial cells. There are 2 types of ET receptors: $ET_A$ and $ET_B$. The $ET_A$ receptors are localized in smooth muscle cells and mediate vasoconstriction and cell growth. In contrast, $ET_B$ receptors are found, above all, in endothelial cells and stimulation leads to vasodilation through release of NO and prostacyclin. The $ET_A$:$ET_B$ ratio in pulmonary arteries is 9:1, and so the net effect of ET release is vasoconstriction and favoring of cell proliferation.

In heart failure, the plasma concentration of ET is elevated and its value closely correlates with mPAP and pulmonary vascular resistance (PVR).[17]

Both factors dependent on endothelial damage (NO reduction and ET increase) are known mediators that, by means of vasoconstriction and cell proliferation, initiate vascular remodeling.

## Histopathology of Pulmonary Hypertension Associated With Left Heart Disease

There are few studies that analyze pulmonary histopathology in chronic pulmonary venous hypertension, and these are old and limited to mitral stenosis.

Microscopic examination of the pulmonary tissue from patients with venous PH shows capillary distension, thickening, and basement membrane rupture and transudation of erythrocytes through the damaged membranes to the alveolar spaces. Often, pulmonary hemosiderosis is observed,
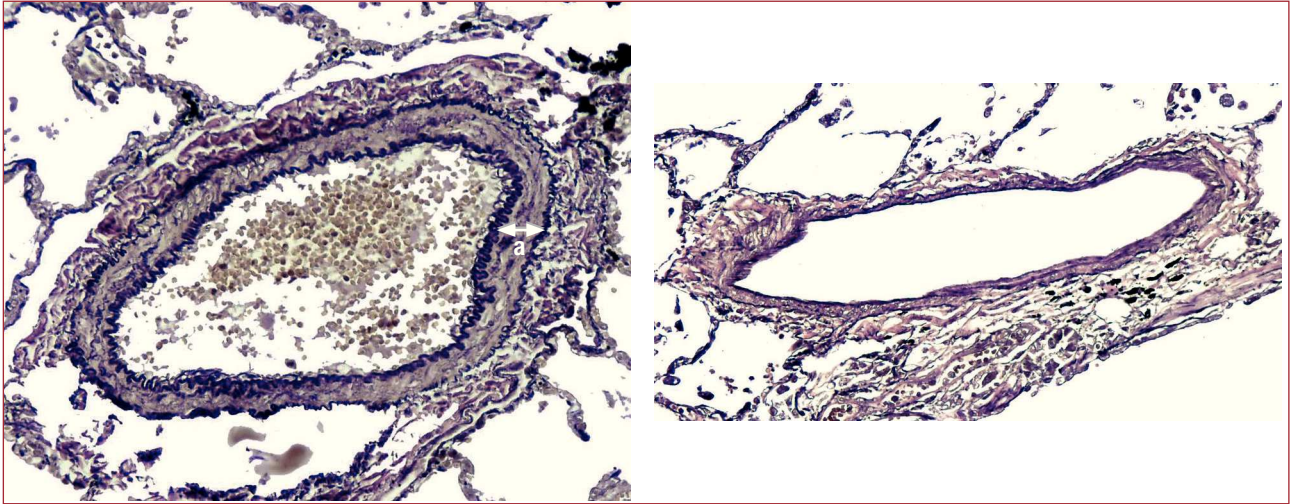
**Figure 3.** Marked medial hypertrophy of a muscular pulmonary artery in a patient with chronic heart failure (left, arrow indicates the medial thickness), compared to another of similar size with minimal medial thickening (right) in a patient with heart failure but not pulmonary hypertension (van Gieson stain, ×100).

and this can progress to marked fibrosis. But the most characteristic changes in pulmonary venous hypertension occur in arteries, veins, and lymph vessels (Table 3). The term used to describe these histopathological changes is congestive vasculopathy and it has been studied above all in mitral valve disease.[18]

The most characteristic arterial changes occur in the muscular pulmonary arteries. The most noteworthy element is medial hypertrophy, which is often severe and generally more extensive than observed in patients with PAH, for comparable degrees of PH.[19]

In mitral stenosis, a close correlation has not been found between the extent of medial hypertrophy and the severity of PH.[20] However, in advanced systolic heart failure, the extent of medial hypertrophy is related to the severity of PH (Figure 3).[21]

Medial hypertrophy of the muscular arteries is associated with arteriolar muscularization. Another arterial factor often present is intimal fibrosis, which is generally eccentric and not obstructive.

In veins and venules, medial hypertrophy occurs and, with this, arterialization of the venous vessels and intimal fibrosis. The lymph vessels show marked dilation, with the appearance of lymphangiectasias, particularly when the venous pressure chronically exceeds 30 mm Hg.

All these structural changes in the pulmonary vessels determine whether PH is reactive and fixed or irreversible. The term fixed or irreversible PH means that the severity of PH is not reduced with vasodilator drugs. As such, the term is useful as it represents an approximation of the severity of PH attributable to

**TABLE 3. Pulmonary Lesions in Congestive Vasculopathy**

| | |
|---|---|
| Pulmonary arteries | Prominent medial hypertrophy and arteriolar muscularization |
| | Intimal fibrosis, generally eccentric and not obstructive |
| Pulmonary veins | Prominent medial hypertrophy and arterialization |
| | Moderate fibrosis of the intima |
| Lymphatic | Dilation |
| Pulmonary tissue | Interstitial edema, interstitial fibrosis, and hemosiderosis |

vascular remodeling. However, the term irreversible is not completely correct because once the cause of venous hypertension has resolved (for example, after heart transplantation in chronic heart failure or after mitral valvuloplasty or valve-replacement surgery in the case of mitral stenosis), a reverse vascular remodeling process is probably initiated because pulmonary pressure tends to normalize months or years after these procedures.[22-26]

In heart failure with normal left ventricular ejection fraction (LVEF), the pathophysiological and histopathological aspects have been a lot less widely studied. However, in a recent population study in which the prevalence of PH in this type of patient was studied by Doppler echocardiography, PH was detected in 83% of patients, and when present, it was often severe. In that same study, it was found that the severity of PH in many cases was disproportionate for the degree of left preload, suggesting a reactive vascular component is at work, as in patients with systolic heart failure.[27]

## DIAGNOSIS OF PULMONARY HYPERTENSION IN HEART FAILURE

The definition of PH associated with heart failure is coupled with the need for a hemodynamic study to confirm that mPAP is ≥25 mm Hg at rest and that PWP is >15 mm Hg.[3]

However, hemodynamic study is not necessary in all cases in which PH associated with heart failure is detected, as echocardiography can provide sufficient information for appropriate clinical management.

In systolic heart failure, echocardiographic findings generally point to an obvious cause of PH. In addition, from tricuspid regurgitation, we can estimate pulmonary systolic pressure and with tissue Doppler studies, using the E/E' ratio, we can obtain a reasonable approximation to the left ventricular filling pressure. Only when it is necessary to accurately determine the severity and/or reversibility of PH (candidate for heart transplantation or ventricular support) is hemodynamic study for this purpose absolutely essential.

However, in a patient with heart failure and normal LVEF, it may be extremely hard to distinguish between PH caused by left-ventricular diastolic dysfunction and PAH. The echocardiographic findings that point to left-ventricular diastolic dysfunction include left ventricular dilation, atrial fibrillation, abnormal left-ventricular filling pattern, and ventricular hypertrophy.[28] In this group of patients, and although the echocardiographic study provides valuable information, sometimes catheterization is necessary to measure PWP or end-diastolic left ventricular pressure to determine whether they are elevated.[28]

Nevertheless, even in cases of left-ventricular diastolic dysfunction, the ventricular filling pressure may be normal, particularly in patients treated with diuretics. Exercise testing or study of volume overload has been proposed to uncover "occult" diastolic dysfunction. However, these tools are not standardized and require better evaluation in order to be validated.[5] On the other hand, in some patients, it might be difficult to distinguish PAH from PH associated with left-ventricular diastolic dysfunction, particularly in those patients with left ventricular preload pressures close to the limit of normal (15-18 mm Hg).[3]

## CLINICAL SIGNIFICANCE OF PULMONARY HYPERTENSION IN PATIENTS WITH HEART FAILURE

In general, PH associated with left-sided heart disease is a factor resulting in a deterioration in functional capacity, with worse prognosis and worse surgical outcomes.

In systolic heart failure, the presence of PH has important functional and prognostic implications.[29,30] There is an inverse relationship between peak oxygen uptake (spirometry during exercise testing) and resting pulmonary arterial pressure. In heart failure, a decrease in systemic vascular resistance occurs during exercise while the PVR remains high. Together, this implies that PH contributes to a reduction in functional capacity through an increase in RV afterload.[31] This hypothesis is based on a close correlation between peak oxygen uptake and the right-ventricular ejection fraction at rest and during exercise.[32]

In addition, PH in heart failure is closely related to inefficient pulmonary ventilation, thereby contributing to exercise-induced hyperpnea and dyspnea in these patients.[33,34]

But PH in patients with systolic heart failure not only contributes to their functional deterioration and influences the clinical situation, it is also associated with worse prognosis and is a variable independent of mortality.[30,35] Probably, the negative impact of PH on survival is due to its impact on RV function, which in turn is an important prognostic marker in advanced heart disease.[36]

Less well known is the clinical significance of PH in patients with heart failure and normal LVEF. Recent data from a population-based sample of 244 patients with heart failure and normal LVEF showed a close relationship between the presence of PH estimated by echocardiography and mortality. When this sample was compared to a control group of hypertense patients with heart failure, the presence of PH had a high predictive value for distinguishing between patients with and without heart failure. In addition, PH in patients with heart failure and normal LVEF was the only echocardiographic variable associated with mortality.[27]

## TREATMENT OF PULMONARY HYPERTENSION IN PATIENTS WITH HEART FAILURE

There is no specific treatment for PH associated with heart failure. Likewise, no drug approved for the treatment of heart failure is contraindicated due to the presence of PH.[3]

In a substantial number of patients, PH associated with systolic heart failure is at least partially reversible with pharmacological treatment, as the passive component is predominant. Thus, optimizing medical treatment (oxygen, diuretics, nitrates, angiotensin converting enzyme [ACE] inhibitors, angiotensin-II receptor antagonists [ARA-II], and β-blockers) and resynchronization therapy significantly reduce PWP and subsequently mPAP.[3,37,38]

Optimization of medical treatment sometimes requires a cycle of inotropic treatment (dobutamine, milrinone, or levosimendan).[39]

However, drugs with a "selective" vasodilatory effect in the pulmonary vascular bed and those that are useful in idiopathic PAH have had a negative or neutral effect on PH secondary to heart failure.

Prostacyclin is very useful in the evaluation of the vasoreactivity of the pulmonary vascular bed in heart failure: it reduces PWP and PVR and increases the cardiac index. However, chronic administration by continuous intravenous infusion increased mortality in treated patients (Flolan International Randomized Survival Trial [FIRST]) by some unknown mechanism.[40]

Inhalation of NO at doses of 5 to 80 parts per million (ppm) in moderate or severe heart failure with associated PH reduces TPG and PVR, but surprisingly does not reduce pulmonary pressure. Moreover, the decrease in TPG is associated with increased left-ventricular filling pressure. Perhaps the selectivity of NO in the pulmonary vascular bed leads to dysfunction in venous return to the left ventricle, and as a result increases the ventricular preload.[41] Thus, inhaled NO is not indicated in the management of PH in patients with heart failure.[42] However, it has been successfully used to assess pulmonary vasoreactivity,[43] as perioperative support in high-risk valve or coronary artery surgery,[44] and for preventing or treating right ventricular heart failure after heart transplantation or after implantation of a left-ventricular support device.[45]

Sildenafil citrate is a potent selective inhibitor of type 5 phosphodiesterase (a widespread enzyme in the pulmonary vascular bed), which induces smooth muscle cell relaxation and causes vasodilation through an increase in cyclic GMP. Its acute hemodynamic effects (oral dose, 50-100 mg) are reduction in mPAP and PVR (to a greater extent than in systemic circulation) without hardly affecting PWP or the cardiac index. These properties make sildenafil a very useful drug for assessing the vasoreactivity of patients with heart failure.[46-48] More recent data have shown that an oral dose of 50 mg of sildenafil improves the functional capacity of patients with systolic heart failure[49] and that chronic treatment for 3 and 6 months improves hemodynamics, functional capacity, and quality of life in these patients.[50,51] Nevertheless, studies are needed that evaluate the mechanism of action of sildenafil in heart failure and that rule out a positive inotropic effect by indirect inhibition of phosphodiesterase 3 (remember that the positive inotropic effect in heart failure is associated with increased mortality), as a step prior to studies designed to assess mortality.[52]

Selective and nonselective ET receptor antagonists (ETRAs) were shown to improve hemodynamics, ventricular remodeling, and survival in animal models of heart failure.[53] However, the clinical results have been disappointing. The most studied ETRA in PH in patients with heart failure is the nonselective antagonist tezosentan (Randomized Intravenous Tezosentan [RITZ] 1, 2, 4, and 5 trials). Administered intravenously at a dose of 50-100 mg/h, it improves hemodynamics but not clinical symptoms or prognosis of acute decompensated heart failure.[54] Perhaps the drug was not been given at an appropriate dose. Recently it has been found that administration of low doses of tezosentan (1-25 mg/h) is hemodynamically active and may lower concentrations of BNP.[55] Although the hemodynamic effects with 1 mg/h are minimal and appear late, they may be persistent. New clinical studies are necessary to confirm that these doses can lead to clinical improvement.

The second nonselective ETRA studied in chronic heart failure and administered orally is bosentan. In the REACH-1 study, 250 mg of bosentan or placebo were administered every 12 hours; the study was terminated prematurely after finding a high incidence of elevated transaminase in the treated group.[56] On terminating the study, there were no significant changes in the clinical status of the treated and untreated patients. In the ENABLE I/II studies, doses of 125 mg/12 h of bosentan or placebo were administered to patients with class III or IV heart failure according to the New York Heart Association. After 9 months of follow-up, no differences in clinical status or mortality were found in the treated group compared to the placebo group.[53]

Darusentan, a selective antagonist of $ET_A$ receptors, was assessed in the HEAT study, and it was found that administration to patients with chronic heart failure improved the cardiac index.[57] However, administration at doses of 10 to 300 mg/day for 6 months (Endothelin Receptor Antagonist Trial in Heart Failure [EARTH] study) did not improve left-ventricular remodeling, clinical symptoms, or prognosis.[58]

Many hypotheses have been proposed to explain the lack of efficacy of ETRA in patients with heart failure. One of these is the inappropriate selection of patients included in clinical trials.[2] It may be that ETRA are effective only in a certain subgroup of patients with chronic heart failure.[59]

In view of the above, and at present, none of the pharmacological treatments that have been shown to be effective in PAH are recommended for patients with systolic heart failure and PH. However, it is very important to continue to research this therapeutic area, particularly with sildenafil and ETRAs. If PH is a marker of poor prognosis in these patients, it is necessary to continue to search for some other

specific effective and safe therapeutic approach, particularly for the subgroup of patients with the most severe forms (disproportionate PH).

In patients with heart failure and normal LVEF, clinical practice guidelines recommend controlling arterial hypertension, prevention of left ventricular hypertrophy or attempting to reverse it through ACE inhibitors or ARA-II, appropriate control of plasma volume by sodium restriction and diuretics, and, finally, prevention of tachyarrhythmia or control of heart rate to optimize diastolic filling time with β-blockers or calcium antagonists. In these patients, modest benefit can be obtained in the reduction admission to hospital by using candersartan.[37] But aside from these general recommendations, there are no data on the influence of specific treatments that have been shown to be effective in PAH for treatment of heart failure in patients with normal LVEF. Currently, the Evaluating the Effectiveness of Sildenafil at Improving Health Outcomes and Exercise Ability in People With Diastolic Heart Failure (RELAX) study is in progress to assess the efficacy of sildenafil in this group of patients.[60]

## MANAGEMENT OF TRANSPLANTATION CANDIDATES WITH ADVANCED HEART FAILURE AND PULMONARY HYPERTENSION

This situation is worthy of special mention, as PH associated with heart failure is a risk factor for mortality or morbidity after heart transplantation, particularly due to early graft failure associated with RV dysfunction.[61-63] And we should bear in mind that early graft failure is the most common cause of death during the first month after transplantation.[64]

TPG >12 mm Hg and/or precapillary PVR >2.5 UW, after vasodilator challenge, are the limits for risk above which the risk of death after heart transplantation increased.[65-70] TPG and PVR above these values show a continuous positive correlation with perioperative mortality, although a limit above which the risk is unacceptable has not be defined.

Although PH is an important risk factor for right ventricular failure after heart transplantation, there are other factors, some of which are dependent on the RV of donor, which influence perioperative outcomes (hemodynamic management of the donor, ischemic damage during preservation, and reperfusion damage after implantation). This would explain why even mild PH can have a deleterious influence on the perioperative outcomes and that patients with more severe PH can undergo transplantation successfully, even with limited hemodynamic repercussions.

In view of the above, in advanced heart failure of the candidate for transplantation, hemodynamic assessment is essential. Before this, it is reasonable to initially optimize the pharmacological treatment for heart failure in accordance with clinical parameters. When significant PH is detected in clinical examination or Doppler echocardiography, a short course lasting 48 to 72 hours of intravenous inotropic treatment can even be considered prior to the initial hemodynamic study.

If the pulmonary pressures exceed the limits for risk in this initial study, study with a vasodilator is recommended.[71] The clinical practice guidelines of the International Society for Heart and Lung Transplantation (ISHLT) recommend conducting a vasodilator challenge if the systolic pulmonary artery pressure (SPAP) is ≥50 mm Hg and TPG is ≥15 mm Hg or PVRs are >3 UW.[72] This is done using nitroglycerin, nitroprussiate, prostaglandin E1, prostacyclin, NO, iloprost, and sildenafil. However, no regimen has been shown to be better than another and so there are no specific recommendations.[3] Likewise, there are no basal hemodynamic parameters that can predict response to a vasodilator challenge; however, low cardiac index and very high PVR (>6 UW) are predictive of poor response.[73]

After vasodilator challenge, a large number of patients are included in the "reversible" PH category and can be put on the waiting list. However, although it is a controversial topic, it seems that prognosis after heart transplantation in this group of patients with reversible PH is slightly unfavorable compared to patients without PH.[74] For hemodynamic vigilance of these patients while they are on the waiting list, it is recommended to perform right heart catheterization every 3 to 6 months.

If the PWP has not decreased below 25 mm Hg and SPAP below 60 mm Hg in the vasodilator challenge, the reversibility of the PH has not been assessed; thus before ruling out heart transplantation for PH, another more effective way of treating the pulmonary congestion should be sought.[72]

On the other hand, if the figures for pulmonary pressure after vasodilator challenge lie within the range of reversibility, but they are associated with a drop in systolic artery pressure below 85 mm Hg, the risk is not reduced after transplantation.[66]

Patients in whom high-risk PH persists after vasodilator challenge may be candidates for intensive pharmacological inotropic and vasodilator treatment (oral and intravenous), as the PH may finally revert to "reversible" PH. This transformation is what some authors have denoted "vasodilator conditioning,"[75] and in this case a therapeutic escalation of inotropic and vasodilator therapy is necessary under hemodynamic monitoring. There is no well-defined regimen, but a combination of selective inotropic and vasodilator agents are considered. With this regimen, it is possible to minimize the number of patients ruled out of heart transplantation for "irreversible" PH.

If high-risk PH persists despite the above approaches, it is possible to add mechanical support devices such as intraaortic counterpulsation balloons and ventricular support devices to pharmacological therapy.[72,76]

Candidates for transplantation with heart failure and "reversible" PH who have required vasodilator challenge need special management. There are, however, no universally recommended approaches although possibilities include 3- or 6-monthly reevaluation of the severity of PH while on the waiting list,[72] maintenance of vasodilator treatment until transplantation,[59] appropriate donor selection (rounding up the weight with respect to the recipient, hemodynamic maintenance with low doses or without inotropic agents, and expected short ischemia time), and, finally, protection of the right ventricle immediately after surgery with NO, intravenous prostacyclin, iloprost, or sildenafil.

Despite applying all the above options, some patients do not attain the limits of PH reversibility that would allow an acceptable risk for orthotopic heart transplantation. According to the clinical practice guidelines of the ISHLT, PVR >5 UW and TPG>16-20 mm Hg, and especially if one of the 2 determinations is concurrent with SPAP >60 mm Hg after the measures described above should be considered a relative contraindication for orthotopic heart transplantation.[72]

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