# Pulmonary hypertension due to left heart disease: Overview of characteristics and its impact on short and long-term prognosis

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## Abstract

**Aim:** To assess the clinical, echocardiographic and laboratory characteristics of pulmonary hypertension (PH) due to left heart diseases (LHDs), and to assess the prognostic role of PH in patients with LHDs.
**Methods:** This study was conducted at the University Hospital Center "Mother Teresa" in Tirana and the Institute of Cardiovascular Emergencies "Prof. C.C Iliescu", Bucharest. The study population included 208 patients, 53.8% female, average age 63.04±11.26 years. Inclusion criteria consisted of pulmonary artery systolic pressure (PASP) $\geq$50 mmHg due to LHDs. Patients were divided into four major groups: patients with left ventricle (LV) systolic dysfunction (N=71), patients with LV diastolic dysfunction (N=35), patients with mitral (N=66) and aortic (N=36) valvulopathies. Anthropometric data, symptoms, blood tests, transthoracic echocardiography, six-minute walking test distance (6MWT), comorbidities and treatment were recorded. Data regarding death were taken from family if death occurred outside hospital. Patients were followed every six months. Average follow-up time was 1.8±1.2 years.
**Results:** PASP correlated will the severity of heart failure (r=0.268, P<0.001) and 6MWT distances (r= - 0.313, P<0.001). There was no significant relationship between PASP and LV ejection fraction (r=0.107, P=0.126). PASP correlated with LV diastolic dysfunction (r=0.206, P=0.034). PASP directly influenced mortality (r=0.348, P<0.001): each unit increase of PASP, increased by 8.5% the probability of death.
**Conclusion:** PH due to LHDs aggravates HF symptoms and reduces physical activity, indifferent of LVEF. PASP is influenced by LV diastolic dysfunction. With its powerful impact on mortality, PH may be considered a marker of primary disease which requires specific treatment.

***Keywords***: heart failure, left heart disease, prognosis, pulmonary hypertension, treatment.

## Introduction

Left heart diseases are currently the most prevalent cause of PH (1), a common complication that negatively impacts symptoms, exercise capacity, and outcome of these patients (2). PH due to LHD is defined as a combination of a mean pulmonary artery hypertension ≥25 mm Hg (mPAP) and a pulmonary artery wedge pressure >15 mm Hg (3). The true prevalence of PH-LHDs is unknown (4). PH can complicate any left heart disorder, such as valvular heart diseases and congenital defects. The current definition of PH due to LHD or group 2 PH include five categories of patients: patients with LV systolic dysfunction, patients with LV diastolic dysfunction, patients with valvular diseases, patients with congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies and patients with congenital /acquired pulmonary veins stenosis (3). However, PH has been most often studied in patients with heart failure with preserved or reduced ejection fraction (6,7).

The underlying pathological mechanism responsible for appearance and negative progression of PH in these patients is almost the same. The hallmark being the elevated left atrial pressure which causes a passive increase in pulmonary pressure and in some cases a superimposed active component caused by pulmonary arterial vasoconstriction and vascular remodeling may lead to a further increase in PASP (5). Most of the published studies have involved patients with strict inclusion criteria and mainly with a specific pathology of the left heart that associate PH. In this way they provide information that is welcome in this field, but without approaching an overview of PH due to LHDs, which in our point of view is very important especially for young doctors who care for these patients on a daily basis. Moreover, despite the large number of patients with PH due to LHDs and their poor prognosis, so far there is no specific treatment which target PH in these patients, making further studies not only necessary but also very welcome. We hope that while providing an overview on the impact of PH due to LHD, we will be able to assist in a better understanding and treatment of this condition.

## Methods

The study included patients with PASP ≥50 mmHg due to LHDs. Patients were divided into 4 major groups: patients with left ventricle systolic dysfunction and PH (71 patients, of them 31% females), patients with left ventricle diastolic dysfunction and PH (35 patients, of them 57.1% females), patients with mitral valvulopathies (66 patients, 72% females) and aortic valvulopathies (36 patients, 61.1% females). We have not included in our study patients with congenital/acquired LHDs, as their incidence and prevalence is small. Patients were hospitalized in the Department of Internal Medicine and Arterial Hypertension in University Hospital "Mother Theresa" in Tirana, Albania, and in the Clinic of Cardiology in Institute of Cardiovascular Emergencies "Prof. C.C Iliescu", Bucharest, Romania. Anthropometric data, symptoms and time of first diagnosis were recorded. ECG and thoracic RX were performed to all patients. Transthoracic echocardiography was recorded by an accredited cardiologist for this examination. All participants in the study underwent blood tests including the pro-BNP, D dimeri, Troponina T, C reactive protein, uric acid. All patients who have been able to carry 6 minute walking test, already did it and the distance was recorded. In patients with clinical or laboratory data suggestive for ischemic heart disease, or those who planned surgical intervention to correct the valvular defect, coronarography was performed. Medication and surgical interventions were notice. All associated diseases were recorded. Data on the location and cause of possible death are taken from family if death occurred outside of hospital. Stable patients under treatment were evaluated every six months with all the above examination. Patients who committed cardiac intervention (especially patients with valvulopathies)

were estimated up to 1 week immediately after surgery and every six months later. This interval was selected as appropriate for the follow-up, considering the high mortality rate in this group of patients based on many studies. Primary End Point of this study was death. Secondary End Point was considerable improvement of health status and PH, needing further medical advice every 2 years. Each patient has been informed of the nature of the study and signed a written consensus to participate in. Average follow-up time was 1.8 ±1.2 years. 15 patients out of 208 (7.2%) could not be followed up through years.

This study was conducted in two large University Hospital Centers with the permission of the concerned authorities to ensure its eligibility. During this study, there were not conducted examinations or experimental procedures that could bear high risk/or unknown risk of complications for the participants. Each patient included in this study agreed with the examinations and the follow-up plan.

***Statistical analysis***

Continuous data were presented as mean values with their respective standard deviations and categorical data were presented in absolute values and their respective percentages. Pearson and Spearman correlation coefficients were used to assess the linear relationship between two numerical variables.

Differences between groups were analyzed by Student's t-test (two groups) and one-way ANOVA (for more than two groups). The differences in proportions were analyzed by chi-square test. P-values $\leq$0.05 were considered as statistically significant.

Binary logistic regression was used to assess the main association of interest, where for each variable, the odds ratios and their respective 95% confidence intervals (CI) were calculated.

Data analysis was performed by use of SPSS 20.0 (Statistical Package for Social Sciences, 20.0).

## Results

Regarding the overall characteristics of the patients included in this study (Table 1), the largest group consisted of patients with LV systolic dysfunction and PH (71). The average age of patients included in the study was 63.04±26.11 years. There was a statistically significant difference in mean age between the study groups (P<0.001). The highest average age was observed in patients with LV diastolic dysfunction (69.63±6.66 years), who also had a higher body mass index than the other groups of patients. There was a statistically significant difference in mean values of PASP between groups (P<0.001). The highest mean value of PASP was recorded in patients with mitral valvulopathies (74.36±18.91 mmHg). Approximately half of the patients with LV systolic dysfunction and mitral valvulopathies had atrial fibrillation, compared with only a third of patients in the other two groups.

Notably, more than two thirds of patients with LV systolic dysfunction associated coronary arteries disease (CAD), compared with more than half of patients with LV diastolic dysfunction and those with aortic valvulopathies. A third of patients with mitral valvulopathies associate coronary artery disease. Most of the patients in group 2 associate severe arterial hypertension and they had the biggest percentage of diabetes mellitus and chronic renal disease, with high significant statistical difference compared with other groups. Regarding the systolic function of the right ventricle in analyzed patients, the smallest value of TAPSE was seen in patients with left ventricle systolic dysfunction. No statistical difference was observed regarding the number of hospitalizations in all groups.

We observed that PASP, in all groups, was well-correlated with the severity of NYHA heart failure functional class (r=0.268, P<0.001) (Figure 1). This fact was supported more strongly by the negative correlation between PASP and 6 minutes walking

test distance (r= - 0.313, P<0.001) and with pro-BNP levels (r=0.143, P=0.039). Also, severity of PASP leads to statistically increased number of hospitalizations (r=0.299, P<0.001).

**Table 1. Overall characteristics of patients included in the study**

| Overall characteristics of the patients | | | | | P-value |
|---|---|---|---|---|---|
| | **Group 1** | **Group 2** | **Group 3** | **Group 4** | |
| **No. of patients** | 71 | 35 | 66 | 36 | |
| **Age** | 64.07±8.67 | 69.63±6.66 | 55.97±13.75 | 67.56±6.71 | <0.001* |
| **Sex (f)** | 31.0% (22) | 57.1%(20) | 72.7%(48) | 61.1%(22) | <0.001† |
| **BMI** | 28.93±4.12 | 31.41±5.76 | 26.65±3.60 | 27.36±3.54 | <0.001* |
| **6MWT** | 171.52±71.54 | 222.06±87.27 | 209.88±94.19 | 224.22±99.17 | <0.001* |
| **HBP (3)** | 36.6% (26) | 85.7%(30) | 36.4%(24) | 52.8%(19) | <0.001† |
| **AF** | 46.5% (33) | 28.6%(10) | 57.6(38) | 33.3%(12) | 0.018† |
| **CAD** | 77.5% (55) | 54.3%(19) | 33.8%(22) | 58.3%(21) | <0.001† |
| **CRD** | 23.9% (17) | 57.1%(20) | 24.2%(16) | 22.8%(8) | 0.001† |
| **DM** | 49.3% (35) | 65.7%(23) | 22.7 %(15) | 25.0%(9) | <0.001† |
| **EF** | 38.18±7.03 | 56.97±10.4 | 54.15±9.34 | 55.58±9.66 | <0.001† |
| **PASP** | 66.38±10.95 | 62.57±9.44 | 74.36±18.9 | 68.14±10.8 | <0.001* |
| **TAPSE** | 15.69±2.91 | 18.41±8.03 | 16.73±3.12 | 19.09±3.51 | <0.001* |
| **Mortality** | 60.3% (38) | 58.1%(18) | 54.2%(22) | 41.2%(14) | 0.327† |
| **Hospital No.** | 2.79±2.04 | 2.66±1.8 | 3.03±2.8 | 2,42±1.72 | 0.478† |

* ANOVA.
† Chi-Square.

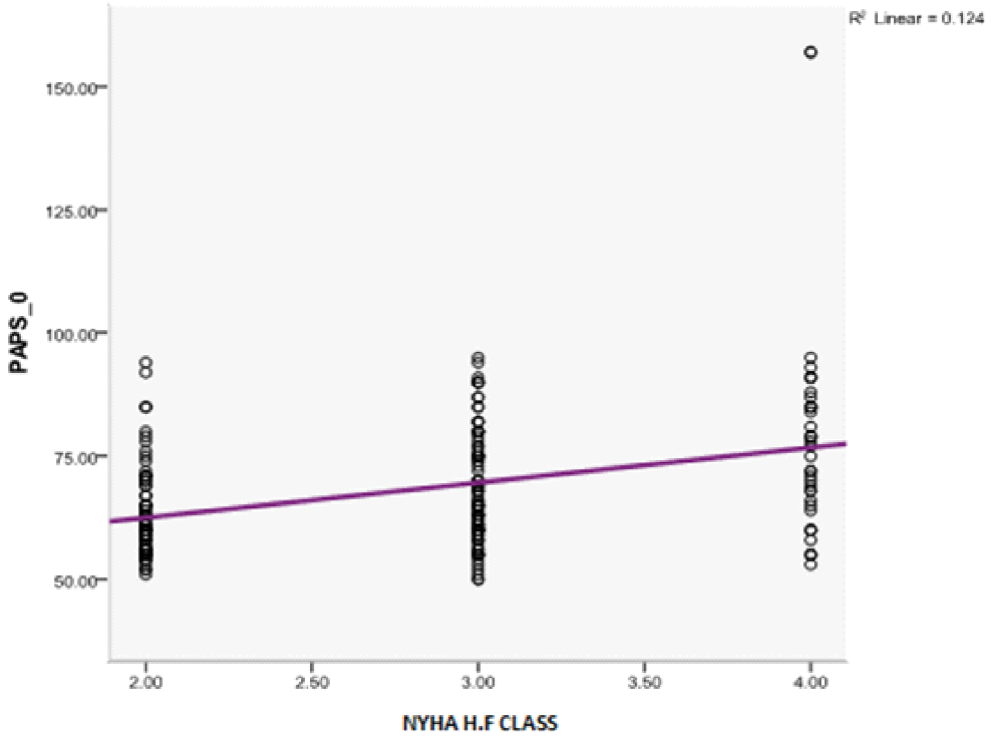
BMI- body mass index, 6MWT- 6 minute walking test, HBP (3)-severe high blood pressure, AF- atrial fibrillation, CAD- coronary artery disease, CRD- chronic renal disease, D.M –diabetes mellitus, EF- ejection fraction, PAsP- pulmonary artery systolic pressure, TAPSE- tricuspid annular plane systolic excursion).

Left ventricle diastolic dysfunction remains one of the most important impact factors of pulmonary hypertension in patients with LHDs. Also, PASP was statistically well-correlated with the severity of diastolic dysfunction (r=0.206, P=0.034), but not with the ratio E / E‘(r=0.101, P=0.149). Furthermore, there was no statistical relationship of PASP with the LVEF (r=0.107, P=0.126).

Regarding the overall mortality of patients included in our study, there was a progressive tendency of mortality during the follow-up period. The highest mortality was recorded in patients with LV systolic dysfunction and PH (60.3%), followed closely by patients with LV diastolic dysfunction (58.1%). More than half of patients in group 1 died in the second year of follow-up (54.0%), while in the third year of study, approximately two-thirds of patients were not alive. The lowest mortality was recorded in patients with aortic (41%) and mitral valvulopathies (54%), especially in those patients who have undergone surgery for valvular correction. However including in these two groups also patients who did not undergo

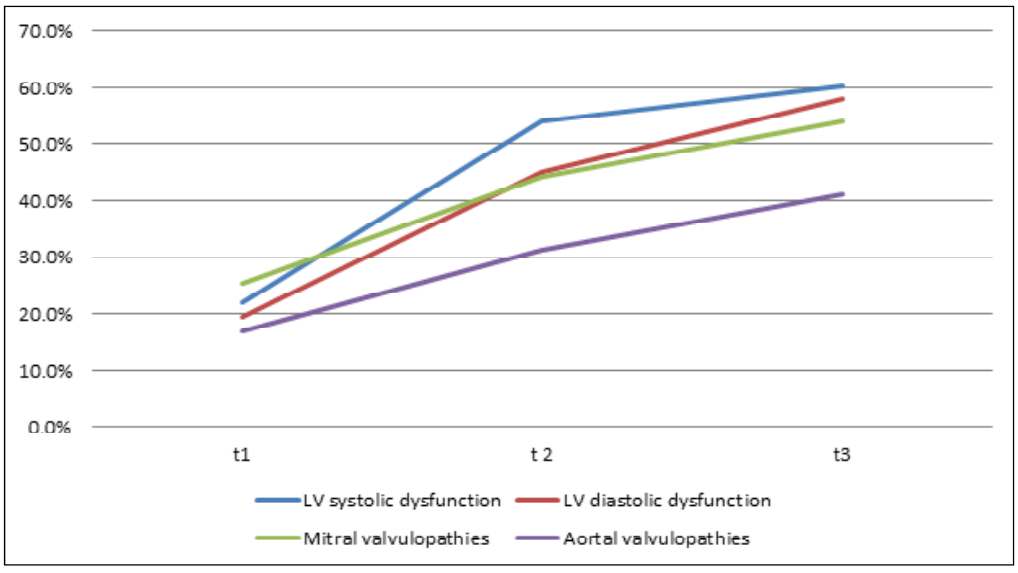
cardiac surgery, the overall mortality remains very high, approaching nearly half of the total patients.

**Figure 1. Correlation between PASP and heart failure NYHA class**




(PASP_0- pulmonary artery systolic pressure, NYHA.H.F.CLASS- NYHA heart failure functional class)

**Figure 2. Mortality trend of all four groups of patients**




Mortality was statistically correlated with the severity of PASP in the whole group of patients (r=0.348, P<0.001), and in different groups of patients, excluding patients from the diastolic

dysfunction group. Using binary logistic regression, there was a strong and statistically significant association between PASPs and mortality (P<0.001), one unit increase of PASP increased by 8.5% the probability of death (Table 2). We also found a direct link between indexed left ventricle telesystolic diameter (LVTSD) and mortality (P=0.009): for every unit increase in the indexed LVTSD, the probability of death increased by 12%.

**Table 2. The impact on mortality of different echocardiographic parameters**

| | Death - year | | | | |
|---|---|---|---|---|---|
| **Variables** | **No (N=151)** | **Yes (N=42)** | **OR** | **95%CI** | **P-value** |
| LVTSD_IND | 21.69±5.4 | 24.14±5.99 | 1.124 | 1.03-1.23 | 0.009 |
| PASP | 66.28±12.82 | 78.57±12.83 | 1.085 | 1.04-1.13 | <0.001 |
| LA_VOLUM | 111.99±46.20 | 137.83±68.99 | 1.004 | 0.99-1.01 | 0.483 |
| Mitral TDE | 169.68±52.82 | 142.62±45.20 | 0.998 | 0.99-1.01 | 0.709 |
| TAPSE | 17.63±3.34 | 14.90±2.96 | 0.917 | 0.79-1.06 | 0.251 |

(LVTSD_IND- indexed telesystolic diameter of left ventricle, PASP-pulmonary artery systolic pressure, LA_VOLUM-left atrial volume, Mitral TDE- deceleration time of mitral wave E, TAPSE-tricuspid annular plane systolic excursion)

## Discussion

Left heart diseases are known as the most frequent cause of PH. It can complicate any left heart disorder, such as valvular heart diseases and congenital defects (1). In our study, we included patients with LHDs and PASP ≥50 mmHg or Peak Tricuspid Regurgitation Velocity >3.4 m/s, which according to the guideline of Diagnosis and Treatment of Pulmonary Hypertension have a high probability of having PH (3). We chose this high threshold of PASP to increase probability of involved patients with truly PH, as we did not perform right cardiac catheterization, a fact which constitutes one of study's limitations. According to numerous studies, echocardiografic evaluation of PASP has good correlation with pressure data approached by right cardiac catheterization (5).

In our view, there is no coincidence that the largest group of patients included LV systolic dysfunction, because referral of these patients from small cities to University Hospital Centers is more frequent compared to patients with LV diastolic dysfunction. The highest average value of PASP was recorded in patients with mitral valvulopathies, with a significant difference compared with others groups. This result is in line with other studies and is understandable if we refer to the direct pressure overload of pulmonary vascular bad caused by mitral valvulopathies (9). As described in the specialized literature, patients with LV diastolic dysfunction and HP are older than those with other PH-LHDs patients (10). This fact is supported by a strong statistical correlation also in our study.

In our study, patients with LV diastolic dysfunction had a greater number and a high percentage of comorbidities, such as severe high blood pressure, obesity, diabetes mellitus and chronic renal disease – a finding which is similar to other studies published in the literature (11). On the other hand, these patients had almost the same mortality with LV systolic dysfunction patients, and it appears that mortality in this group is not influenced by severity of PASP as in all other groups. In this context, we assume that high mortality in patients with LV diastolic dysfunction is influenced by the large number of associated diseases and the lack of rapid diagnosis.

Coronary artery disease was a frequent finding in our group of patients. More than two thirds of

patients with HP and LV systolic dysfunction and over half of the patients with LV diastolic dysfunction and aortic valvulopathies had CAD. In this context it seems logical that for patients with HP and LV systolic dysfunction, coronarography should be introduced in the standard examinations of care, indifferent to the presence of symptoms suggestive of CAD.

Pulmonary hypertension aggravates symptoms of heart failure and reduces the quality of life in patients with LHDs. Our statistical results are in line with those from other studies, observing that PASP, in all studies groups, is well correlated with the severity of NYHA heart failure functional class (12). The highest the value of PASP, the highest pro-BNP levels and the smallest 6MWT distance, in our patients cohort. Based on the statistical analysis, we observed that patients with severe PH had aggravated heart failure with an increase of pro-BNP levels and a reduced ability to walk. This clinical profile fully justifies high statistical correlation between PASP and the number of hospitalization of our study.

Research has focused on the exploration of possible causes of PH in patients with LHDs. Their conclusions are parallel with the results of our study, highlighting once again the fact that PASP is influenced by LV diastolic dysfunction but not by LV filling pressure which could be influenced by medication (13). Also, as in other studies in the literature, we noted that PASP is not statistically related to LVEF (14).

Overall mortality of our patients has an up-progressive tendency during all follow up periods. As in other studies, we recorded the highest mortality in patients with LV systolic dysfunction and PH followed closely by patients with LV diastolic dysfunction (15). More than half of patients in group 1 died in the second year of follow-up while in the third year of study, approximately two-thirds of patients were not alive. The smallest mortality was recorded in patients with aortic and mitral valvulopathies especially in those patients who have undergone surgery for valvular correction, such therapy having a positive impact over PASP resolution. However, including in these two groups also patients who did not undergo cardiac surgery, the overall mortality remains very high, approaching nearly half of the total patients.

Mortality was statistically correlated with the severity of PASP in the whole group of patients and in different groups of patients, excluding patients from the diastolic dysfunction group. Using binary logistic regression we observed that there was a strong and statistically significant association between PASPs and mortality, where one unit increase of PASP increased by 8.5% the death probability. This finding is in line with a previous study and suggests that PH could not be only a complication of LHDs, but rather an important factor leading to the deterioration of the clinic state and prognosis of primary left cardiac disease (16).

***Study limitations***

Our patients did not perform right heart catheterization and data on pulmonary pressures are obtained by transthoracic echocardiography. PASP measured by this method has been shown in many studies that correlates well with the one measured by right heart catheterization (8).

Also, it was not possible to measure E- Endothelin and other factors of inflammation and vascular remodeling but we have notes a good statistical correlation between the severity of PH and PCR and Uric Acid. Many of the patients with LV systolic dysfunction and HP had indication for cardiac transplant and could benefit from the left ventricular assisting devices as bridge therapy until cardiac transplant, procedures that are not currently carried out in Albania. This fact may justify the higher mortality of these patients compared with other international published studies (1).

## Conclusion

Pulmonary hypertension due to LHD is a factor that leads to further progression of the primary disease and heart failure symptoms. PH affects negatively the possibility of active life of these patients. It has a very important prognostic role, being an important prognostic index. Mortality in patients with PH, especially in patients with systolic or diastolic left ventricular dysfunction, despite treatment, makes the further studies indispensable which should target specifically the treatment of HP in these patients and not just treatment of primary left heart disease. Taking into consideration the mortality that PH bears in patients with LHD, it cannot be considered just a complication of the disease, but rather a marker of disease progression and bad prognosis.

**Conflicts of interest**: None declared.

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