



# The role of left atrial function in severe precapillary pulmonary arterial hypertension: clinical and hemodynamic perspectives

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## Abstract

**Objective:** The study aimed to investigate the clinical, structural, and hemodynamic characteristics of patients with pulmonary arterial hypertension (PAH) in relation to mean left atrial (LA) pressure.

**Methods:** 58 patients with precapillary PAH were prospectively enrolled and stratified into two groups based on mean LA pressure assessed by transthoracic echocardiography: Group 1 (<8 mmHg) and Group 2 (>8 mmHg). All patients underwent clinical evaluation, right heart catheterization, echocardiography including LA strain and stiffness analysis.

**Results:** Patients in Group 2 were older ( $55.96 \pm 2.52$  vs  $41.4 \pm 2.53$  years,  $p < 0.001$ ), had a higher burden of left heart comorbidities, and demonstrated more advanced LA myopathy with significantly impaired reservoir ( $20.03 \pm 2.37$  vs  $31.42 \pm 2.21\%$ ,  $p = 0.0014$ ), conduit ( $13.91 \pm 1.78$  vs  $18.52 \pm 1.48\%$ ,  $p = 0.053$ ), and contractile strain ( $7.96 \pm 1.26$  vs  $16.41 \pm 1.56\%$ ,  $p < 0.001$ ). Despite more favorable markers of heart failure compensation (NT-proBNP levels:  $888.81 \pm 216.06$  vs  $2187.34 \pm 707.11$  pg/mL,  $p = 0.050$ ), they exhibited worse exercise tolerance on the 6MWT ( $294.39 \pm 18.80$  vs  $349.68 \pm 19.05$  m,  $p = 0.047$ ). Hemodynamically, RV dysfunction in Group 1 was predominantly driven by the resistive component of afterload, while in Group 2 both resistive and pulsatile components were involved.

**Conclusions:** Patients with severe precapillary PAH and elevated mean LA pressure represent a distinct clinical phenotype characterized by significant LA dysfunction and a combined hemodynamic burden. These findings underscore the need for personalized diagnostic approaches that account for the complex interactions between pulmonary vascular disease and left-heart pathology.

## Keywords

Pulmonary arterial hypertension, left atrial pressure, left atrial myopathy, right ventricular failure, pulmonary vascular resistance.

## Rezumat

**Obiectiv:** Studiul a avut ca scop investigarea caracteristicilor clinice, structurale și hemodinamice ale pacienților cu hipertensiune arterială pulmonară (HAP) în raport cu presiunea medie atrială stângă (AS).

**Metode:** 58 de pacienți cu HAP pre-capilară au fost incluși prospectiv și stratificați în două grupuri în funcție de presiunea medie atrială stângă evaluată prin ecocardiografie transtoracică: Grupul 1 (<8 mmHg) și Grupul 2 (>8 mmHg). Toți pacienții au fost supuși evaluării clinice, cateterismului cardiac drept și ecocardiografiei, inclusiv analiza deformării și rigidității atrului stâng.

**Rezultate:** Pacienții din Grupul 2 erau mai în vârstă ( $55,96 \pm 2,52$  vs.  $41,4 \pm 2,53$  ani,  $p < 0,001$ ), aveau o povară mai mare de comorbidități ale inimii stângi și au prezentat o miopatie atrială stângă mai avansată, cu afectarea semnificativă a deformării de rezervor ( $20,03 \pm 2,37$  vs.  $31,42 \pm 2,21\%$ ,  $p = 0,0014$ ), de conducere ( $13,91 \pm 1,78$  vs.  $18,52 \pm 1,48\%$ ,  $p = 0,053$ ) și contractile ( $7,96 \pm 1,26$  vs.  $16,41 \pm 1,56\%$ ,  $p < 0,001$ ). În ciuda markerilor mai favorabili de compensare a insuficienței cardiace (niveluri NT-proBNP  $888,81 \pm 216,06$  vs.  $2187,34 \pm 707,11$  pg/mL,  $p = 0,050$ ), aceștia au prezentat o toleranță la efort mai redusă la testul de mers pe 6 minute ( $294,39 \pm 18,80$  vs.  $349,68 \pm 19,05$  m,  $p = 0,047$ ). Din punct de vedere hemodinamic, disfuncția ventriculului drept în Grupul 1 a fost determinată predominant de componenta rezistivă a încărcării post-sarcină, în timp ce în Grupul 2 au fost implicate atât componentele rezistive, cât și cele pulsatile.

## Concluzii:

Pacienții cu HAP pre-capilară severă și presiune medie atrială stângă crescută reprezintă un fenotip clinic distinct, caracterizat prin disfuncție atrială stângă semnificativă și o povară hemodinamică combinată. Aceste rezultate subliniază necesitatea unor abordări diagnostice personalizate care să țină cont de interacțiunea complexă dintre boala vasculară pulmonară și patologia inimii stângi.

## Cuvinte cheie

Hipertensiune arterială pulmonară, presiune atrială stângă, miopatie atrială stângă, insuficiență ventriculară dreaptă, rezistență vasculară pulmonară

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## Introduction

Pulmonary arterial hypertension (PAH) is a condition characterized by elevated pulmonary artery pressure, which can lead to right ventricular (RV) failure and death [1]. Over the past 35 years, registry data indicate that the mean age of patients with PAH has increased from  $36 \pm 15$  to  $52 \pm 15$  years [2, 3]. As a result, the number of patients with PAH and concomitant cardiovascular diseases involving the left heart chambers has risen. COMPERA and ASPIRE registry data revealed that patients with idiopathic PAH (IPAH) with cardiovascular comorbidities ("atypical IPAH") share features of both typical IPAH and PH associated with heart failure and preserved ejection fraction (HFpEF), suggesting that there may be a continuum between these conditions [4]. Later experts of the Cologne Consensus Conference introduced two new terms: "typical IPAH" and "atypical IPAH" [5].

Most studies on typical PAH have focused on RV function to identify markers of transition from adaptive to maladaptive remodeling under increased pulmonary vascular resistance (PVR) [6]. As PAH progresses, the dilated right heart chambers compress the left chambers, impairing left ventricular (LV) compliance, reducing diastolic filling, and consequently decreasing cardiac output [7, 8]. These changes necessitate a shift in focus from solely RV parameters to a comprehensive evaluation of interventricular, interatrial, and atrioventricular interactions. This underscores the need to expand research beyond right ventricular function alone, toward a more integrated assessment of interventricular, interatrial, and atrioventricular dynamics—including the role of the left atrium (LA) in cardiovascular adaptation in PAH.

In patients with PAH and concomitant cardiovascular diseases, additional pathophysiological mechanisms commonly associated with left-sided heart failure—such as left ventricular diastolic dysfunction and progressive remodeling of the LA—play a significant role [9, 10]. In HFpEF, compensatory responses, including systemic venous constriction and structural changes within the LA, aim to elevate its pressure and sustain cardiac output [11]. However, in PAH, elevated PVR and pathological right-to-left ventricular interaction disrupt these compensatory mechanisms, contributing to a complex pathophysiology and clinical presentation. The contribution of the LA function within this interaction remains inadequately understood.

**The aim of this study** was to investigate the clinical, structural, and hemodynamic characteristics of patients with severe precapillary PAH and varying LA pressures.

## Methods

This prospective, single-center study enrolled 58 patients with precapillary PAH who were under regular follow-up at the Department of Internal Medicine 3, Communal Enterprise "Dnipro Regional Clinical Centre of Diagnostics and Treatment." The diagnosis of PAH was established according to the 2022 European Society of Cardiology (ESC) guidelines [1].

Patients were stratified into two groups based on mean LA pressure estimated by transthoracic echocardiography (TTE):

Group 1: mean LA pressure  $< 8$  mmHg

Group 2: mean LA pressure  $> 8$  mmHg

The cutoff value of 8 mmHg was based on the work of Braunwald et al., who in 1961 first reported invasive measurements of mean LA pressure ranging from 2 to 12 mmHg, with an average of 7.9 mmHg. This threshold has since been validated in several subsequent studies [12].

All patients underwent a comprehensive clinical evaluation, including detailed medical history, vital signs, a 6-minute walk test (6MWT), and measurement of N-terminal pro-brain natriuretic peptide (NT-proBNP).

TTE was performed using a Vivid E9 expert-class ultrasound system (GE Healthcare, USA). Structural and functional parameters of both right and left heart chambers were assessed in accordance with the recommendations of the European Association of Cardiovascular Imaging and the 2025 ASE guidelines for the echocardiographic evaluation of the right heart, including special considerations for pulmonary hypertension [13–15].

Mean LA pressure was estimated using pulsed-wave and tissue Doppler imaging according to the following validated formula:

$$\text{mean LA pressure} = 1.24 \times E/E' + 1.9$$

This approach, originally proposed by Nagueh et al., has demonstrated excellent correlation between Doppler-derived estimates and invasive measurements of pulmonary artery wedge pressure (PAWP), which reflects the cumulative hemodynamic influence of LA pressure throughout the cardiac cycle [16].

LA strain—including reservoir, conduit, and contractile phases—was assessed using speckle-tracking echocardiography based on current guidelines from the European Association of Cardiovascular Imaging and the American Society of Echocardiography [17–19].

All patients underwent right heart catheterization to obtain invasive hemodynamic measurements. Comorbidities, including arterial hypertension and volume status, were optimally managed before the procedure. The external pressure transducer was zeroed at the mid-thoracic level in the supine position. All pressures, including PAWP, were recorded at end-expiration without breath-holding. Cardiac output (CO) was measured using the thermodilution method via cold saline injection, with the average of at least three measurements used for analysis. Intracardiac shunts were excluded clinically and/or echocardiographically.

Precapillary PAH was defined as:

- mean pulmonary arterial pressure (mPAP)  $> 20$  mmHg,
- PAWP  $< 15$  mmHg,
- PVR  $> 3$  Wood units at rest [1, 20].

Additional hemodynamic parameters included:

- $PVR = (mPAP - PAWP) / CO$  [1]
- Pulmonary artery capacitance (PAC) = stroke volume (SV) / (systolic PAP – diastolic PAP) [21]
- Pulmonary artery elastance (PAE) =  $0.9 \times \text{systolic PAP} / SV$  [22, 23]
- Pulmonary artery pulsatility index (PAPi) = (systolic PAP – diastolic PAP) / right atrial pressure [24]

Table 1 - Clinical Characteristics of Patients with Precapillary Pulmonary Arterial Hypertension Stratified by Mean LA Pressure.

| Parameter                           | Group 1 (n=32)   | Group 2 (n=27)  | p-value |
|-------------------------------------|------------------|-----------------|---------|
| Age, years                          | 41.4 ± 2.53      | 55.96 ± 2.52    | 0.000   |
| Gender (male/female)                | 8 / 24           | 4 / 23          | 0.324   |
| BMI, kg/m <sup>2</sup>              | 25.4 ± 1.31      | 28.5 ± 1.38     | 0.106   |
| IPAH                                | 21 (65.6%)       | 23 (85.2%)      | 0.072   |
| PAH-CTD                             | 4 (12.5%)        | 3 (11.1%)       | 0.868   |
| PAH-HIV                             | 5 (15.6%)        | 1 (3.7%)        | 0.112   |
| PAH-CHD                             | 2 (6.3%)         | 0               | 0.148   |
| Hypothyroidism                      | 2 (6.3%)         | 7 (25.9%)       | 0.043   |
| DM / Glucose intolerance            | 3 (9.3%)         | 4 (14.8%)       | 0.523   |
| Peptic ulcer                        | 4 (12.5%)        | 3 (11.1%)       | 0.868   |
| Psoriasis                           | 0                | 2 (7.4%)        | 0.147   |
| Arterial hypertension (Stage 1)     | 2 (6.3%)         | 2 (7.4%)        | 0.869   |
| Arterial hypertension (Stage 2–3)   | 7 (21.8%)        | 13 (48.1%)      | 0.034   |
| Stenting                            | 0                | 4 (14.8%)       | 0.035   |
| Myocardial infarction (unconfirmed) | 0                | 4 (14.8%)       | 0.035   |
| Chronic coronary syndrome           | 4 (12.5%)        | 2 (7.4%)        | 0.511   |
| Atrial fibrillation                 | 0                | 8 (29.6%)       | 0.001   |
| Ablation for AF                     | 0                | 5 (18.5%)       | 0.016   |
| Euvolemia                           | 10 (31.2%)       | 6 (22.2%)       | 0.435   |
| Mild hypervolemia                   | 5 (15.6%)        | 5 (18.5%)       | 0.769   |
| Moderate hypervolemia               | 8 (25.0%)        | 10 (37.0%)      | 0.323   |
| Severe hypervolemia                 | 6 (18.7%)        | 4 (14.8%)       | 0.689   |
| LHD comorbid stage (Low)            | 17 (53.1%)       | 24 (88.8%)      | 0.002   |
| LHD comorbid stage (Intermediate)   | 10 (58.8%)       | 5 (20.8%)       | 0.013   |
| LHD comorbid stage (High)           | 4 (23.5%)        | 9 (37.5%)       | 0.839   |
| 6-MWT, m                            | 349.68 ± 19.05   | 294.39 ± 18.80  | 0.047   |
| NT-proBNP, pg/ml                    | 2187.34 ± 707.11 | 888.81 ± 216.06 | 0.050   |
| Loop diuretics                      | 30 (93.7%)       | 27 (100%)       | 0.150   |
| MRA                                 | 32 (100%)        | 27 (100%)       | –       |

Abbreviations: BMI – body mass index; DM – diabetes mellitus; IPAH – idiopathic pulmonary arterial hypertension; PAH-CTD – PAH associated with connective tissue disease; PAH-HIV – PAH associated with HIV infection; PAH-CHD – PAH associated with congenital heart disease; LHD – left heart disease; AF – atrial fibrillation; 6-MWT – 6-minute walking test; NT-proBNP – N-terminal pro-brain natriuretic peptide; MRA – mineralocorticoid receptor antagonist

- **Right ventricular stroke work index (RVSWI) = (mPAP – mean RA pressure) × stroke index (SI) × 0.0136 [25]**
- **Right ventricular function (RVF) index = systolic PAP / cardiac index [26]**

Statistical analysis was performed using STATISTICA 10.0 software (StatSoft, USA). Continuous variables are presented as means ± standard deviations or medians with interquartile ranges (25th–75th percentiles), depending on distribution. Between-group comparisons were performed using the Mann–Whitney U test or Student's t-test for independent and dependent samples, as appropriate. The chi-square test was used for categorical variables.

## Results

**Baseline Characteristics:** A total of 58 patients with precapillary PAH were included, with a predominance of women (77.6%). The mean age was 49.2 ± 2.06 years. The majority of patients had idiopathic PAH (IPAH, 74.1%). Other etiologies included PAH

associated with connective tissue disease (12.0%), HIV (8.6%), and congenital heart disease (3.4%).

Based on the mean LA pressure measured by echocardiography, patients were divided into:

- **Group 1** (n = 32): mean LA pressure <8 mmHg
- **Group 2** (n = 27): mean LA pressure >8 mmHg

Clinical characteristics are presented in Table 1.

Group 2 patients were significantly older (55.96 ± 2.52 vs. 41.4 ± 2.53 years,  $p < 0.001$ ), with no significant differences in sex or body mass index. Comorbidities such as hypothyroidism ( $p = 0.043$ ), stage 2–3 arterial hypertension ( $p = 0.034$ ), ischemic heart disease ( $p = 0.035$ ), and atrial fibrillation ( $p = 0.001$ ) were significantly more prevalent in Group 2. The proportion of patients with left heart disease comorbidities was also higher (88.8% vs. 53.1%,  $p = 0.002$ ).

Group 1 patients had better exercise tolerance on the 6-minute walk test (349.68 ± 19.05 vs. 294.39 ± 18.80 m,  $p = 0.047$ ), but paradoxically higher NT-proBNP levels (2187.34 ± 707.11 vs. 888.81 ± 216.06 pg/mL,  $p = 0.050$ ).

Table 2 - Structural and Functional Characteristics of Myocardium in Patients with Precapillary Pulmonary Arterial Hypertension.

| Parameter                                     | Group 1 (n=32) | Group 2 (n=27) | p-value |
|-----------------------------------------------|----------------|----------------|---------|
| LV eccentricity index                         | 1.69 ± 0.08    | 1.68 ± 0.10    | 0.960   |
| PA diameter, mm                               | 30.1 ± 1.17    | 31.27 ± 2.36   | 0.661   |
| Sm cor                                        | 10.2 ± 0.6     | 11.24 ± 0.82   | 0.298   |
| TAPSE, mm                                     | 16.17 ± 1.18   | 20.05 ± 1.29   | 0.032   |
| RA ESA index, cm <sup>2</sup> /m <sup>2</sup> | 11.38 ± 0.77   | 11.34 ± 0.72   | 0.736   |
| RA EDA index, cm <sup>2</sup> /m <sup>2</sup> | 9.63 ± 0.84    | 9.22 ± 0.75    | 0.721   |
| LA ESA index, cm <sup>2</sup> /m <sup>2</sup> | 7.26 ± 0.27    | 9.06 ± 0.61    | 0.012   |
| LA EDA index, cm <sup>2</sup> /m <sup>2</sup> | 6.16 ± 0.28    | 7.35 ± 0.47    | 0.036   |
| LA ESA ≤ EDA                                  | 14 (43.7%)     | 9 (33.3%)      | 0.413   |
| LA ESV index, mL/m <sup>2</sup>               | 16.37 ± 1.08   | 25.09 ± 2.80   | 0.007   |
| LA EDV index, mL/m <sup>2</sup>               | 13.0 ± 1.07    | 17.94 ± 1.94   | 0.033   |
| RV EDV index, mL/m <sup>2</sup>               | 49.94 ± 4.60   | 47.33 ± 5.01   | 0.703   |
| LV EDV index, mL/m <sup>2</sup>               | 43.04 ± 2.73   | 44.47 ± 3.47   | 0.748   |
| LV EF, %                                      | 58.86 ± 2.88   | 52.62 ± 3.02   | 0.163   |
| RV/LV EDV index                               | 1.44 ± 0.19    | 1.29 ± 0.21    | 0.614   |
| RV/ LV CO                                     | 2.36 ± 0.25    | 1.97 ± 0.27    | 0.289   |
| LV SV, mL                                     | 56.31 ± 6.75   | 81.73 ± 12.24  | 0.079   |
| LASr, %                                       | 31.42 ± 2.21   | 20.03 ± 2.37   | 0.0014  |
| LAScd, %                                      | 18.52 ± 1.48   | 13.91 ± 1.78   | 0.053   |
| LASct, %                                      | 16.41 ± 1.56   | 7.96 ± 1.26    | 0.000   |
| LA stiffness                                  | 0.25 ± 0.05    | 0.72 ± 0.19    | 0.037   |

Abbreviations: LV – left ventricle; RV – right ventricle; RA – right atrium; LA – left atrium; EDV – end-diastolic volume; ESV – end-systolic volume; EDA – end-diastolic area; ESA – end-systolic area; EF – ejection fraction; SV – stroke volume; CO – cardiac output; TAPSE – tricuspid annular plane systolic excursion; Sm cor – corrected peak systolic velocity of the tricuspid annulus; LASr – left atrial reservoir strain; LAScd – left atrial conduit strain; LASct – left atrial contraction strain.

**Structural and functional characteristics:** Echocardiographic assessment revealed comparable right atrial dimensions between groups. However, LA volumes and areas were significantly higher in Group 2, indicating more advanced structural remodeling. These data are summarized in Table 2.

TAPSE was significantly greater in Group 2 (20.05 ± 1.29 mm vs. 16.17 ± 1.18 mm,  $p = 0.032$ ), suggesting preserved longitudinal RV function. Despite this, no significant differences were observed in more integrative indices of RV function, such as RVSWI ( $p = 0.853$ ) or RVF index ( $p = 0.161$ ).

Group 2 also demonstrated a trend toward higher LV stroke volume (81.73 ± 12.24 vs. 56.31 ± 6.75 mL,  $p = 0.079$ ), possibly reflecting increased preload.

**Left atrial function:** Speckle-tracking echocardiography showed significant impairment in LA reservoir (20.03 ± 2.37 vs 31.42 ± 2.21%,  $p = 0.0014$ ), conduit (13.91 ± 1.78 vs. 18.52 ± 1.48%,  $p = 0.053$ ), and contractile strain (7.96 ± 1.26 vs. 16.41 ± 1.56%,  $p < 0.001$ ) in Group 2. LA stiffness was also markedly higher (0.72 ± 0.19 vs. 0.25 ± 0.05,  $p = 0.037$ ), confirming the presence of LA myopathy in patients with elevated LA pressure.

**Hemodynamics:** Right heart catheterization data are presented in Table 3. PVR was significantly higher in Group 1 (13.45 ± 1.34 vs. 9.56 ± 1.24 Wood units,  $p = 0.038$ ), as was PAE (1.73 ± 0.16 vs. 1.30 ± 0.14 mmHg/mL,  $p = 0.048$ ), indicating increased vascular stiffness and static afterload.

Other parameters such as mPAP, PAWP, CO, SvO<sub>2</sub>, PAC, and PAPindex did not differ significantly between groups.

## Discussion

This study demonstrates that patients with severe precapillary PAH exhibit distinct clinical and pathophysiological profiles depending on mean LA pressure. Individuals with elevated LA pressure were older, had a higher prevalence of left-heart comorbidities, and were more frequently characterized by advanced LA myopathy—reduced reservoir, conduit, and contractile function—than those with normal LA pressure.

One of the most intriguing findings was the paradoxically lower exercise tolerance in patients with elevated LA pressure (Group 2), despite their better markers of systemic congestion control and a trend toward higher LV SV. This counterintuitive observation highlights the potential impact of LA mechanical dysfunction and diastolic uncoupling on functional limitation. Notably, LA pressure elevation often precedes overt signs of HF decompensation. Our data suggest that many Group 2 patients exhibit disproportionate LA myopathy—evidenced by significantly impaired LA contractile strain and a high frequency of atrial fibrillation ablation history—indicating primary atrial involvement that is not solely secondary to LV dysfunction.

This dissociation supports the concept of a “disproportional atrial myopathy”, where atrial mechanical failure plays a dominant role in symptom onset, independently of LV diastolic severity. Loss of atrial contraction in this setting compromises LV filling and contributes to acute dyspnea and exercise intolerance—even at relatively modest elevations in LA pressure.

Table 3 - Hemodynamic Characteristics of Patients with Precapillary Pulmonary Arterial Hypertension.

| Parameter                             | Group 1 (n=32) | Group 2 (n=27) | p-value |
|---------------------------------------|----------------|----------------|---------|
| mPAP, mmHg                            | 58.16 ± 2.96   | 52.04 ± 3.23   | 0.169   |
| PAWP, mmHg                            | 9.82 ± 0.54    | 11.29 ± 0.64   | 0.092   |
| PVR, Wood units                       | 13.45 ± 1.34   | 9.56 ± 1.24    | 0.038   |
| CO, L/min                             | 4.20 ± 0.28    | 4.85 ± 0.33    | 0.132   |
| SvO <sub>2</sub> , %                  | 65.49 ± 1.85   | 66.89 ± 1.79   | 0.588   |
| PAC, mL/mmHg                          | 1.35 ± 0.17    | 1.64 ± 0.25    | 0.352   |
| PAE, mmHg/mL                          | 1.73 ± 0.16    | 1.30 ± 0.14    | 0.048   |
| PAPi                                  | 5.27 ± 0.69    | 7.46 ± 1.27    | 0.138   |
| RVSWI, g/m <sup>2</sup> /beat         | 19.95 ± 1.66   | 20.42 ± 1.94   | 0.853   |
| RVF index, mmHg/L/beat/m <sup>2</sup> | 42.83 ± 3.36   | 36.14 ± 3.30   | 0.161   |

Abbreviations: mPAP – mean pulmonary arterial pressure; PAWP – pulmonary artery wedge pressure; PVR – pulmonary vascular resistance; CO – cardiac output; SvO<sub>2</sub> – mixed venous oxygen saturation; PAC – pulmonary artery capacitance; PAE – pulmonary artery elastance; PAPi – pulmonary artery pulsatility index; RVSWI – right ventricular stroke work index; RVF index – right ventricular function index.

This observation also provides a potential explanation for the lower NT-proBNP levels observed in Group 2. Although NT-proBNP is classically associated with increased cardiac wall stress, in precapillary PAH it predominantly reflects RV strain and ventricular–arterial uncoupling. In Group 2, where pulsatile load and LA dysfunction predominate, the RV may be relatively less stressed than in Group 1. Consequently, despite greater symptom burden, lower NT-proBNP levels may reflect preserved RV stroke work in the context of isolated LA failure, rather than reduced overall disease severity. In patients with reduced LA compliance and borderline cardiac output, even minor atrial dysfunction can provoke symptoms that appear disproportionate to measured hemodynamics [10].

Hemodynamically, Group 1 was distinguished by significantly higher PVR and PAE, whereas Group 2 exhibited a trend toward increased PAWP. Despite these differences, mPAP, CO, and indices of RV function—including RVSWI and RVF index—did not differ significantly between groups. These findings suggest a comparable degree of RV maladaptation, though driven by distinct components of afterload.

The pulmonary circulation is uniquely characterized by an inverse relationship between resistive and pulsatile load components [27, 34]. In our study, both groups had similar PAC. Still, the greater PAE reduction in Group 1 supports the predominance of the static (resistive) component of RV afterload in patients with normal LA pressure. In contrast, Group 2 patients—despite a relatively higher PAWP—appeared to have a mixed afterload profile, with both resistive and pulsatile components.

Prior research by Tedford et al. [35] in over 8,000 patients undergoing right heart catheterization showed that elevations in PAWP have a disproportionately negative impact on PAC, regardless of PVR, highlighting a distinct pathway by which LV diastolic dysfunction imposes load on the RV via pulsatility. Our findings are consistent with this mechanism: in Group 2, a relatively higher PAWP did not translate into lower PAC, suggesting that, in these patients, pulsatile afterload alone may not dominate, and resistive vascular remodeling remains significant even in the presence of left-heart comorbidities.

**Overlap of Pathophysiological Phenotypes:** taken together, these results support the view that in patients with severe precapillary PAH, elements traditionally ascribed to both Group 1 and Group 2 PH may coexist. Rather than representing isolated disease entities, pulmonary vascular remodeling and left heart pathology appear to interact—clinically and hemodynamically. In the presence of comorbidities such as hypertension, atrial fibrillation, and structural LA disease, it becomes increasingly difficult to distinguish true precapillary disease from an atypical or transitional phenotype.

This diagnostic ambiguity has important clinical implications. While current ESC guidelines prioritize a binary classification of PH (pre- vs. postcapillary) for treatment decisions, our findings underscore the limitations of rigid categorization. For instance, although Group 2 had more frequent occurrences of advanced hypertension and atrial fibrillation, the overall comorbidity burden—when assessed using recommended scoring algorithms—differed only modestly between groups.

Such observations support a more nuanced, phenotype-based classification approach, particularly in older patients with cardiovascular risk factors. The presence of LA myopathy with only mild or borderline LV diastolic dysfunction challenges the assumption that elevated LA pressure necessarily reflects passive transmission from the ventricle. Rather, in such patients, LA structural and mechanical failure may play a primary pathophysiological role.

**Clinical implications and future directions:** This study represents an important step toward a deeper understanding of left heart involvement in patients with severe precapillary PAH. Our findings indicate that in patients with normal mean LA pressure, RV dysfunction is primarily driven by a high resistive load. **In contrast, in** those with elevated LA pressure, both resistive and pulsatile components contribute to right HF. This distinction highlights the heterogeneity of RV afterload even within a clinically similar PAH cohort.

A potential clinical application of these findings is the non-invasive assessment of LA pressure and LA longitudinal strain, which may help identify patients with disproportionate atrial myopathy or early signs of left heart contribution to RV dysfunction. In this context, LA strain imaging—specifically, reservoir and contractile components—

may serve as sensitive markers of atrial mechanical failure and could become key parameters in refined phenotyping.

Importantly, such detailed phenotyping may improve patient selection for PAH-specific therapy, especially in individuals with comorbid conditions that blur the lines between Group 1 and Group 2 PH. The development of individualized diagnostic algorithms, incorporating structural and functional echocardiographic data alongside hemodynamics, could better reflect the true pathophysiological spectrum of disease.

In light of our results, a binary classification framework (pre- vs. postcapillary) may be insufficient for guiding therapy and prognostication in this patient population. We advocate for a personalized, mechanism-based approach that integrates right- and left-heart interactions to improve disease characterization and inform more targeted management strategies.

## Limitations

This study was a prospective, single-center analysis with a relatively small sample size, which may limit the statistical power and generalizability of the findings to the broader population with severe precapillary PAH. While strict inclusion criteria ensured a homogeneous cohort by enrolling only patients with precapillary PAH (as defined by current ESC/ERS guidelines), this came at the expense of external validity. As such, the results should primarily be interpreted as hypothesis-generating, and validation in larger, multicenter cohorts is warranted.

A second limitation is the classification of patients based on non-invasive estimation of mean left atrial pressure. Although the formula proposed by Nagueh et al. ( $\text{mean PAWP} = 1.24 \times E/E' + 1.9$ ) is widely accepted and recommended in the 2025 ASE guidelines for the echocardiographic assessment of right heart and pulmonary hypertension, it remains an indirect estimation. While the method is feasible, reproducible, and predictive of elevated filling pressures when the ratio exceeds conventional thresholds ( $<8$  or  $>15$ ), in our study, we deliberately used it to capture even mild elevations in LA pressure—reflecting our focus on early or subclinical atrial dysfunction. Invasive hemodynamic measurements and echocardiographic assessment were performed within a short interval, but not simultaneously, which may introduce variability.

At the time of study design, the 2015 ESC/ERS guidelines did not recommend volume or exercise challenge during right heart catheterization as part of the standard diagnostic algorithm; therefore, such provocative tests were not performed.

Lastly, the presence of cardiovascular comorbidities in many patients could have led to pharmacological interactions or confounding effects, particularly in the interpretation of strain-based measurements and natriuretic peptide levels.

## Conclusions

1. Non-invasive estimation of left atrial pressure using echocardiographic Doppler indices and left atrial strain

imaging provides valuable insight into the phenotypic diversity of patients with severe precapillary pulmonary arterial hypertension, offering a potential tool for more accurate disease stratification.

2. Patients with elevated mean left atrial pressure tend to be older, have a higher burden of left heart comorbidities, and exhibit more severe left atrial mechanical dysfunction, characterized by reduced reservoir, conduit, and contractile strain—indicating disproportionate atrial myopathy.
3. Despite similar or better markers of hemodynamic compensation, these patients demonstrate reduced exercise capacity, suggesting that left atrial dysfunction and impaired atrioventricular coupling contribute significantly to clinical symptoms—independently of right ventricle output or NT-proBNP levels.
4. Distinct hemodynamic patterns of right ventricular afterload were identified: in patients with normal left atrial pressure, right ventricular dysfunction appears to be primarily driven by elevated pulmonary vascular resistance and vascular stiffness, whereas in patients with elevated left atrial pressure, both resistive and pulsatile components of afterload contribute to right ventricular strain.
5. These findings highlight the limitations of a binary classification model (pre- vs. postcapillary pulmonary hypertension) and support the need for a personalized, mechanism-based approach to phenotyping and managing patients with pulmonary arterial hypertension and cardiovascular comorbidities.

## Contributors

Kalashnykova Oksana – research, formal analysis, writing, original draft;

Vasilyeva Larisa – methodology, writing, review, and editing.

Pertseva Tetyana – conceptualization, research, writing, review, and editing.

## Conflict of interest

None to declare.

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## Consent

The authors confirm that informed written consent was obtained for the submission and publication of this original article.

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