DOI: 10.1002/pul2.12391

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

# Left main coronary artery compression in precapillary pulmonary hypertension

**Ruxandra Badea**[1] | **Roxana Enache**[1,2] | **Lucian M. Predescu**[1,2] | **Pavel Platon**[2] | **Nicu Catana**[2] | **Dan Deleanu**[2] | **Andrei George Iosifescu**[1,2] | **Noela Radu**[1] | **Teodora Radu**[2] | **Georgiana Olaru-Lego**[2] | **Ioan M. Coman**[1,2] | **Bogdan A. Popescu**[1,2]

[1]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

[2]Cardiology Department, 'Prof. Dr. C.C. Iliescu' Emergency Institute for Cardiovascular Diseases, Bucharest, Romania

**Correspondence**
Roxana Enache, 'Carol Davila' University of Medicine and Pharmacy, Soseaua Fundeni 258, PO 022322, Bucharest, Romania.
Email: roxenache@gmail.com

**Funding information**
None

## Abstract

Pulmonary hypertension (PH) is a progressive and invalidating condition despite available therapy. Addressing complications such as left main coronary artery compression (LMCo) due to the dilated pulmonary artery (PA) may improve symptoms and survival. Nevertheless, clear recommendations are lacking. The aim of this study is to analyze the prevalence, characteristics, predictive factors and impact of LMCo in a heterogenous precapillary PH population in a single referral center. Two hundred sixty-five adults with various etiologies of precapillary PH at catheterization were reviewed. Coronary angiography (CA) was performed for LMCo suspicion. Revascularization was performed in selected cases. Outcomes were assessed at a mean follow-up of 3.9 years. LMCo was suspected in 125 patients and confirmed in 39 (31.2%), of whom 21 (16.8%) had 50%–90% stenoses. Nine revascularizations were performed, with clinical improvement. The only periprocedural complication was a stent migration. LMCo was associated with PH etiology (p 0.003), occuring more frequently in congenital heart disease-associated PH (61.5% of all LMCo cases, 66.6% of LMCo ≥ 50%). Predictors of LMCo ≥50% were PA ≥ 37.5 mm (Sn 81%, Sp 74%) and PA-to-aorta ≥1.24 (Sn 81%, Sp 69%), with increased discrimination when considering RV end-diastolic area. LMCo ≥ 50% without revascularization presented clinical deterioration and worse survival (p 0.019). This analysis of a heterogeneous pre-capillary PH population provides LMCo prevalence estimation, predictive factors (PA size, PA-to-aorta, RV end-diastolic area and PH etiology) and long-term impact. While LMCo impact on survival is inconclusive, untreated LMCo ≥ 50% has worse prognosis. LMCo revascularization may be performed safely and with good outcomes.

**KEYWORDS**
extrinsic stenosis, mechanical complications, revascularization

## INTRODUCTION

For rare diseases such as pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) collecting data from clinical trials and registries is essential to proper decision-making, especially when addressing uncommon specific complications as the left main coronary artery compression (LMCo) due to the dilated main pulmonary artery (PA).

PAH is defined by alterations in the precapillary pulmonary tree with high PA pressures and resistance. Etiology ranges from idiopathic (iPAH) and heritable (HPAH) to PAH associated to: congenital heart disease (CHD), drugs, connective tissue disease (CTD), HIV infection, portal hypertension. CTEPH implies post-thromboembolic fibrotic obstructions and it represents a different group of pulmonary hypertension (PH), potentially reversible after surgery. PH groups 1 (PAH) and 4 (CTEPH) and some cases of multifactorial PH (group 5) are considered precapillary PH if PA wedge pressure ≤15 mmHg.[1,2]

A main complication of PH is PA dilation, which is progressive and leads to other complications by compressing adjacent structures. One of these complications, LMCo, not only contributes to excess morbi-mortality (angina, acute coronary syndromes, ventricular dysfunction, arrhythmia, death), but is reversible through interventional or surgical correction, with accumulating data on good outcomes.[3–6] After decades of literature on LMCo and extrapolating management from atherosclerosis, specific recommendations still lack in recent PH guidelines.[1] Our study aims to assess LMCo prevalence, characteristics, predictors, prognosis and management in a real-life cohort of precapillary PH patients receiving pulmonary vasodilators in a PH referral center, with a long-term follow-up.

## METHODS

### Study design

The study population consisted of all adult patients with precapillary PH confirmed at right heart catheterization (cath) included in a PH referral center from 2006 until June 2023. Precapillary PH etiology included groups 1 and 4 and selected cases from group 5. Groups 2 (PH associated with left heart disease) and 3 (PH caused by lung diseases and/or hypoxia) have different pathophysiology from group 1 PH, even when some cases may be apparently similar in haemodynamics, and they are traditionally not amenable to pulmonary vasodilators. Consequently these patients rarely had indication for cath in our PH Center, invasive data being acquired only in cases where cath was especially relevant (i.e. unclear PH mechanism, or before surgery). Specific therapy was withled in patients with severe "cardiopulmonary comorbidities" and/or in patients with PVR < 2 Wood units or PA wedge pressure >15 mmHg because of possible detrimental effects. This population was excluded from our study.[1]

Complete PH assessment was perfomed at enrollment including demographic and clinical data, transthoracic and if indicated transoesophageal echocardiography, left- and right-heart cath with vasoreactivity testing if indicated, lung scintigraphy, chest computed tomography (CT), pulmonary function tests and laboratory studies. Pulmonary vasodilators were administered according to PH Guidelines.[1]

Coronary angiography (CA) was performed in patients with suspected LMCo (eg angina-like symptoms, aneurysmal PA, left ventricular dysfunction, cardiovascular (CV) risk factors (significant systemic hypertension or dyslipidemia, diabetes mellitus, obesity, smoking history), or before surgical interventions—septal defect closure or pulmonary endarterectomy, PEA). Aneurysmal PA was defined as an increase in size larger than 1.5x upper normal limit (in line with other papers we used the cut-off of 40 mm).[7] LMCo was defined as ostial LM stenosis with downward vessel displacement and pencil-tip shape (Figure 1).[7,8] Two subgroup analyses were performed: (1) any grade of LMCo versus no LMCo as control group (Table 1) and (2) LMCo ≥ 50% versus no/mild LMCo as control group (Table 2). In lack of specific recommendations, patients with LMCo ≥ 50% were discussed for revascularization in Heart Team including the attending PH specialist (in our center—a clinician cardiologist), interventional cardiologist, cardiovascular surgeon and intensive care specialist. If agreed upon, patient informed written consent was obtained before interventional or surgical procedures.

Follow-up was systematic according to PH guidelines, every 3 months (with individual strategies if needed): symptoms assessment, clinical examination, 6-min walking test (6MWT) and laboratory work-up.[1] Echocardiography was performed according to EACVI and ASE recommendations at every 6 months or more frequently if needed.[9] Main PA was measured in parasternal short axis view modified for best visualization, at end-diastole, by drawing a line perpendicular to its long axis, from the virtual center of the ascending aorta or next to the LM, using the inner edge-to-inner edge method (Figure 2). This diameter was compared to the ascending aorta for PA/aorta ratio.[9–11] Although all patients underwent chest CT at enrollment, this investigation was not always relevant for PA size and also not

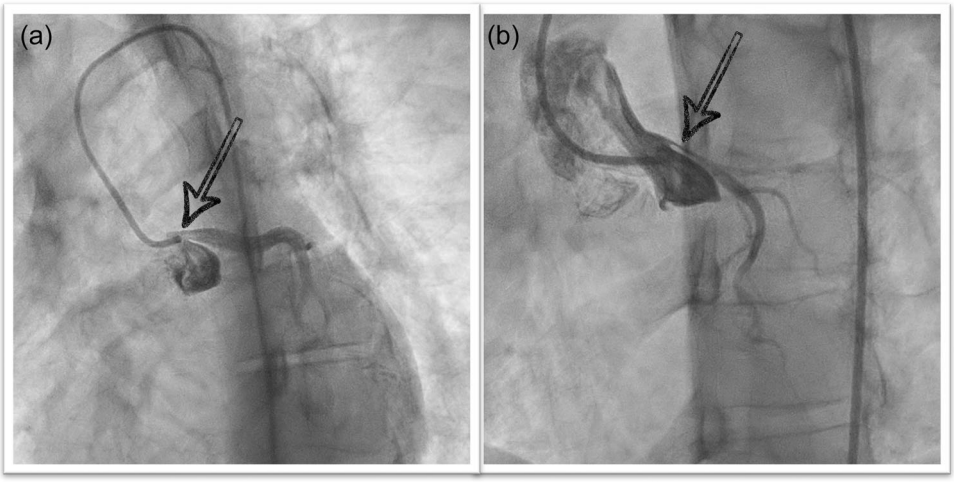


**FIGURE 1** Coronary angiography showing typical characteristics of left main coronary artery compression (arrows): a pencil-tip shaped stenosis with decreasing caliber towards the left main ostium with downward vessel displacement due to compressive effect of the dilated main pulmonary artery. (a) 65% left main stenosis, (b) subocclusive left main stenosis.

readily available at follow-up, so this study reports PA size at echocardiography.[11–17]

Clinical worsening and change of risk-group prompted repeat cath and therapy adjusting.[1] CA was also repeated if indicated. Outcomes were represented by a composite end-point of CV death/clinical worsening.

## Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v. 29.0.1.0 (171). Descriptive data is reported as frequencies (n) and percentages (%), mean ± standard deviation or median accordingly (considering the (non-)normal distribution). Longitudinal data on time-to-event is reported with central tendency and 95% confidence intervals (CI).

Associations between discrete variables were tested using chi-square tests and, according to the expected cell counts and the size of the contingency table, the appropriate alpha value was determined (Fisher, Pearson or likelihood ratio); if necessary, the Bonferroni correction was applied. Associations that included continuous variables were tested using independent samples (student) T-test; when comparing groups the significance was determined using the Levene test. For all associations and predictions an alpha value (2 tails $p$) <0.05 was considered significant.

Logistic regression was used for testing possible predictors of LMCo. Significant predictors at the multivariable analysis were evaluated using receiver-operating characteristic (ROC) analysis; coordinates on sensitivity (Sn) and specificity (Sp) and Youden's index were considered to determine the best cut-offs for LMCo prediction.

Survival rates were calculated using Kaplan-Meier analysis and differences in the bivariate curves were tested for significance with pairwise log rank comparisons. For the multivariable survival analysis and time to other events the Cox proportional hazards model was used to determine significant predictors.

Primary outcome was a composite endpoint of CV death/clinical worsening and secondary outcome was clinical worsening. Univariable analysis was performed for clinical, echocardiographic and cath data as independent variables for outcomes. Those with $p < 0.1$ were included in backwards elimination stepwise regression to identify the independent significant variables.

# RESULTS

## Descriptive statistics for the entire study population

Out of 265 adult patients, 125 patients (47.2%) underwent CA screening for LMCo. There were 81 (64.8%) females, mean age was 48.5 ± 14.7 (18-76) years. Mean body surface area was 1.77 ± 0.25 $m^2$ and body mass index 26.1 ± 5.5 $kg/m^2$. Sixty (48%) patients had CV risk factors or significant comorbidities. At enrollment mean heart rate (HR) was 80.1 ± 12.6 bpm, systolic/diastolic blood pressure (BP) was 118.8 ± 19.7/74.3 ± 12.3 mmHg and spontaneous $SpO_2$ at rest was 85.3 ± 12.0%. For statistical purposes we classified heart failure (HF) into a mild group (WHO functional classes I and II, $n = 34$ [27.2%]) and advanced HF (WHO functional classes III and IV, $n = 91$ [72.8%]). Nineteen (15.2%) patients had

**TABLE 1** Associations from first subgroup analysis: "no LMCo" versus "any LMCo".

| Total population ($n = 125$), data at enrollment | No LMCo ($n = 86$, 68.8%) | Any LMCo (20%–90% stenoses) ($n = 39$, 31.2%) | $p$ value |
|---|---|---|---|
| Age (years) | 49.7 ± 14.9 | 45.8 ± 13.9 | 0.178 |
| Female ($n = 81$) | 52 (64.2%) | 29 (35.8%) | 0.132 |
| PH type | | | |
| – iPAH ($n = 21$) | 19, 22.1% | 2, 5.1% | 0.003 |
| – CHD ($n = 47$) | 23, 26.7% | 24, 61.5% | |
| – CTEPH ($n = 29$) | 23, 26.7% | 6, 15.4% | |
| – CTD ($n = 12$) | 10, 11.6% | 2, 5.1% | |
| – other ($n = 16$) | 11, 12.8% | 5, 12.8% | |
| Chest pain ($n = 19$) | 11 (57.9%) | 8 (42.1%) | 0.265 |
| Other symptoms[a] ($n = 44$) | 32 (72.7%) | 12 (27.3%) | 0.485 |
| WHO groups | | | |
| – I-II ($n = 34$) | 18 (20.9%) | 16 (41%) | 0.018 |
| – III–IV ($n = 91$) | 68 (79.1%) | 23 (59%) | |
| LnBNP (pg/ml) | 5.13 ± 1.38 | 4.67 ± 1.53 | 0.142 |
| 6MWT - Distance (m) | 324.6 ± 140.6 | 350.1 ± 122.2 | 0.369 |
| Pretest $SpO_2$(%) | 82.9 ± 13.6 | 82.3 ± 11.7 | 0.800 |
| Diff. $SpO_2$ (pretest-posttest) (%) | 6.6 ± 8.60 | 5.03 ± 5.46 | 0.367 |
| Invasive data: | | | 0.215 |
| mPAP (mmHg) | 53.9 ± 15.1 | 58.1 ± 18.1 | 0.215 |
| PVR (Wood units) | 10.4 ± 5.9 | 11.4 ± 8.3 | 0.493 |
| Cardiac index (L/min/$m^2$) | 2.33 ± 0.7 | 2.14 ± 0.7 | 0.225 |
| Qp/Qs | 1.23 ± 0.6 | 1.86 ± 1.2 | 0.016 |
| Echocardiographic parameters | | | |
| Main PA (mm) | 34.4 ± 6.7 | 43.1 ± 11.1 | <0.001 |
| PA/aorta | 1.1 ± 0.2 | 1.5 ± 0.4 | <0.001 |
| Tricuspid regurgitation velocity | 4.56 ± 1.5 m/s | 4.59 ± 0.5 m/s | 0.919 |
| RV-EDA ($cm^2$) | 30.0 ± 9.2 | 36.2 ± 11.9 | 0.025 |
| RV-ESA ($cm^2$) | 20.4 ± 7.7 | 24.1 ± 9.2 | 0.089 |
| RV function | | | |
| – RV-FAC (%) | 31.9 ± 9.9 | 33.4 ± 7.4 | 0.513 |
| – RV-GLS (%) | −12.8 ± 5.2 | −12.7 ± 4.4 | 0.921 |
| – TAPSE (mm) | 17.6 ± 4.5 | 18.6 ± 4.3 | 0.335 |
| – RV-S' (cm/s) | 10.3 ± 2.7 | 11.2 ± 2.1 | 0.143 |
| LVEF (%) | 57.1 ± 8.3 | 58.7 ± 5.3 | 0.248 |

Abbreviations: BNP, brain natriuretic peptide; CHD, congenital heart disease; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; Diff. SpO2, difference between oxygen saturation before and after the 6-min-walk-test; iPAH, idiopathic PAH; LMCo, left main coronary artery compression; LVEF, left ventricle ejection fraction; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; Qp/Qs, pulmonary-to-systemic flow ratio; PA, pulmonary artery; PVR, pulmonary vascular resistence; RV, right ventricle; RV-EDA, RV-enddiastolic area; RV-ESA, RV-endsystolic area; RV-FAC, RV fractional area change; RV-GLS, RV global longitudinal strain; RV-S', RV free wall velocity; SpO2, peripheral oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; WHO, World Health Organization; 6MWT, 6-min-walk-test.

[a]Other symptoms=syncope, haemoptysis, ventricular/supraventricular arrhythmia.

**TABLE 2** Associations from second subgroup analysis: "no/mild LMCo" versus "significant LMCo".

| Total population ($n = 125$), data at enrollment | No/mild LMCo (stenoses 0%–49%) $n = 104$ (83.2%) | Significant LMCo (stenoses ≥50%) $n = 21$ (16.8%) | $p$ value |
|---|---|---|---|
| Age (years) | 49.2 ± 14.8 | 44.7 ± 13.7 | 0.199 |
| Female ($n = 81$) | 67 (82.7%) | 14 (17.3%) | 0.528 |
| PH type | | | |
| – iPAH ($n = 21$) | 19 (18.2%) | 2 (9.5%) | 0.035 |
| – CHD ($n = 47$) | 33 (31.7%) | 14 (66.6%) | |
| – CTEPH ($n = 29$) | 25 (24.1%) | 4 (19.1%) | |
| – CTD ($n = 12$) | 12 (11.5%) | 0 (0%) | |
| – other ($n = 16$) | 15 (14.4%) | 1 (4.7%) | |
| WHO groups | | | |
| – I–II ($n = 34$) | –27 (26%) | – 7 (33.3%) | 0.328 |
| – III–IV ($n = 91$) | –77 (74%) | – 14 (66.7%) | |
| LnBNP (pg/ml) | 5.14 ± 1.41 | 4.07 ± 1.25 | 0.008 |
| Angina ($n = 19$) | 14 (73.7%) | 5 (26.3%) | 0.228 |
| Other symptoms[a] ($n = 44$) | 38 (86.4%) | 6 (13.6%) | 0.486 |
| 6MWT - Distance (m) | 324.0 ± 139.7 | 377.3 ± 99.0 | 0.068 |
| Pretest $SpO_2$(%) | 84.9 ± 12.6 | 87.3 ± 6.9 | 0.501 |
| Diff. SpO2 (pretest-posttest) (%) | 6.51 ± 8.21 | 3.93 ± 4.39 | 0.255 |
| Invasive data: | | | |
| mPAP (mmHg) | 55.3 ± 15.8 | 54.9 ± 19.2 | 0.931 |
| PVR (Wood units) | 10.96 ± 6.91 | 8.74 ± 4.77 | 0.249 |
| Qp/Qs | 1.34 ± 0.74 | 1.91 ± 1.35 | 0.178 |
| $SvO_2$ (%) | 64.6 ± 10.7 | 76.7 ± 8.3 | <0.001 |
| Echocardiographic parameters | | | |
| Main PA (mm) | 35.1 ± 7.1 | 46.4 ± 11.9 | <0.001 |
| PA/aorta | 1.15 ± 0.26 | 1.56 ± 0.42 | <0.001 |
| Tricuspid regurgitation velocity | 4.55 ± 1.42 m/s | 4.65 ± 0.51 m/s | 0.755 |
| RV-EDA($cm^2$) | 30.2 ± 8.7 | 39.6 ± 13.9 | 0.041 |
| RV-ESA ($cm^2$) | 20.4 ± 7.4 | 26.2 ± 10.6 | 0.081 |
| LVEF (%) | 57.2 ± 7.8 | 59.3 ± 5.9 | 0.255 |

Abbreviations: BNP, brain natriuretic peptide; CHD, congenital heart disease; CTD, connective tissue disease; CTEPH; chronic thromboembolic pulmonary hypertension; Diff. SpO2, difference between oxygen saturation before and after the 6-min-walk-test; iPAH, idiopathic PAH; LMCo, left main coronary artery compression; LVEF, left ventricle ejection fraction; mPAP, mean pulmonary artery pressure; PH, pulmonary hypertension; Qp/Qs, pulmonary-to-systemic flow ratio; PA, pulmonary artery; PVR, pulmonary vascular resistence; RV, right ventricle; RV-EDA, RV-enddiastolic area; RV-ESA, RV-endsystolic area; SpO2, peripheral oxygen saturation; SvO2, mixed venous oxygen saturation; WHO, World Health Organization; 6MWT, 6-min-walk-test.

[a]Other symptoms = Syncope, haemoptysis, ventricular or supraventricular arrhythmia.

chest pain and 44 (35.2%) other symptoms (syncope, haemoptysis, ventricular or supraventricular arrhythmias). Mean LnBNP was 4.99 ± 1.43 pg/ml, distance at 6-min-walking test (6MWT) was 332.4 ± 135.2 m.

Twenty-one patients (16.8%) had iPAH, 47 (37.6%) CHD-PAH, 29 (23.2%) CTEPH, 12 (9.6%) CTD-PAH, and 16 (12.8%) had other types of precapillary PH amenable to pulmonary vasodilators (drug-induced, HIV infection,

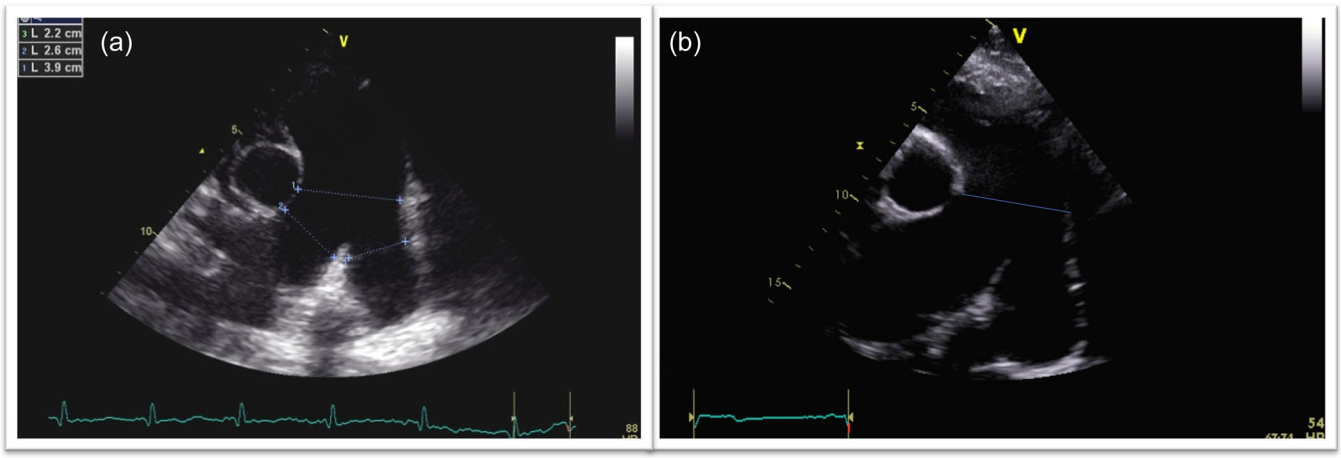


**FIGURE 2** Main pulmonary artery (PA) measurement at 2D transthoracic echocardiography, parasternal short axis view modified for best PA visualization. (a) Moderately dilated main PA 39 mm, right PA 26 mm, left PA 22 mm. (b) Aneurysmal main PA 61 mm.

porto-pulmonary or multifactorial). Mean PA pressure (mPAP) at cath was 55.2 ± 16.3 mmHg, mean pulmonary vascular resistance (PVR) 10.7 ± 6.7 Wood units (Wu), mean cardiac index 2.27 ± 0.7 L/min/m$^2$. Echocardiography showed mean PA size of 37.3 ± 9.4 mm, mean PA-to-aorta ratio (PA/aorta) 1.2 ± 0.3, mean tricuspid regurgitation velocity 4.6 ± 1.3 m/s.

LMCo of any severity was confirmed in 39 (31.2%) patients, 21 (16.8%) having 50-90% stenoses. At the end of individual follow-up 50 (40%) patients were on PH specific monotherapy (pulmonary vasodilators), 70 (56%) on combination therapy and two were surgically corrected CTEPH. The remaining three cases did not adhere to therapy or were lost to follow-up.

## First subgroup analysis—no LMCo versus any grade of LMCo (stenoses of 20%–90%)

When comparing demographic data between patients with any grade of LMCo stenosis (severity range 20%–90%, 39 [31.2%] patients) and no LMCo (controls, 86 [68.8%] patients), they differed in types of PH etiology (p 0.003, maintaining significance after Bonferroni correction) and WHO functional class (p 0.018). Cath revealed a higher Qp/Qs in the LMCo subgroup (1.86 ± 1.2 vs. 1.23 ± 0.6, p 0.016) but no other significant associations, for instance no difference in $SvO_2$ (p 0.12). At echocardiography any LMCo was associated with larger PA size and PA/aorta ratio (both $p < 0.001$). Patients with any LMCo also had larger RV end-diastolic area (p 0.025), but RV end-systolic area and RV fractional area change were similar.

Supplemental data on associations between clinical, hemodynamic and imaging variables at enrollment for no versus any LMCo are displayed in Table 1.

## Second subgroup analysis—no/mild LMCo (stenoses 0%–49%) versus significant LMCo (stenoses ≥50%)

When comparing demographic data between patients with significant LMCo (stenosis ≥50%, 21 [16.8%] patients) and no/mild LMCo (controls, 104 [83.2%] patients) again the only difference was in PH etiology (p 0.035). In this analysis LMCo ≥ 50% was associated with lnBNP (p 0.008), but the association did not remain significant when adjusting for WHO class. Cath revealed a higher $SvO_2$ in the LMCo ≥ 50% subgroup (76.7 ± 8.3 vs. 64.6 ± 10.7, $p < 0.001$) but no other significant associations, for instance no difference in Qp/Qs (p 0.178). At echocardiography LMCo ≥ 50% was associated with larger PA size and PA/aorta ratio (both $p < 0.001$). Patients with LMCo ≥ 50% also had larger RV end-diastolic area (p 0.041), but RV end-systolic area was similar.

Supplemental data on associations between clinical, hemodynamic and imaging variables at enrollment for no/mild LMCo versus significant LMCo are displayed in Table 2.

## Predictors for LMCo

LMCo (both "any stenosis" and "significant stenosis ≥50%") was associated with PH etiology (p 0.003 and 0.035 respectively), specifically with CHD. No associations were found with any other clinical parameters, with emphasis on chest pain (AUC 0.56 for "any LMCo," p 0.38).

The best imaging parameters to predict "any LMCo" were PA diameter and PA/aorta ratio, with AUC 0.754 (95% CI 0.65–0.85) and 0.803 (95% CI 0.71–0.89) respectively, both $p < 0.001$. (Figure 3a). When predicting LMCo ≥ 50%, the AUC was 0.81 for PA size (95% CI 0.71–0.92) and 0.82 for

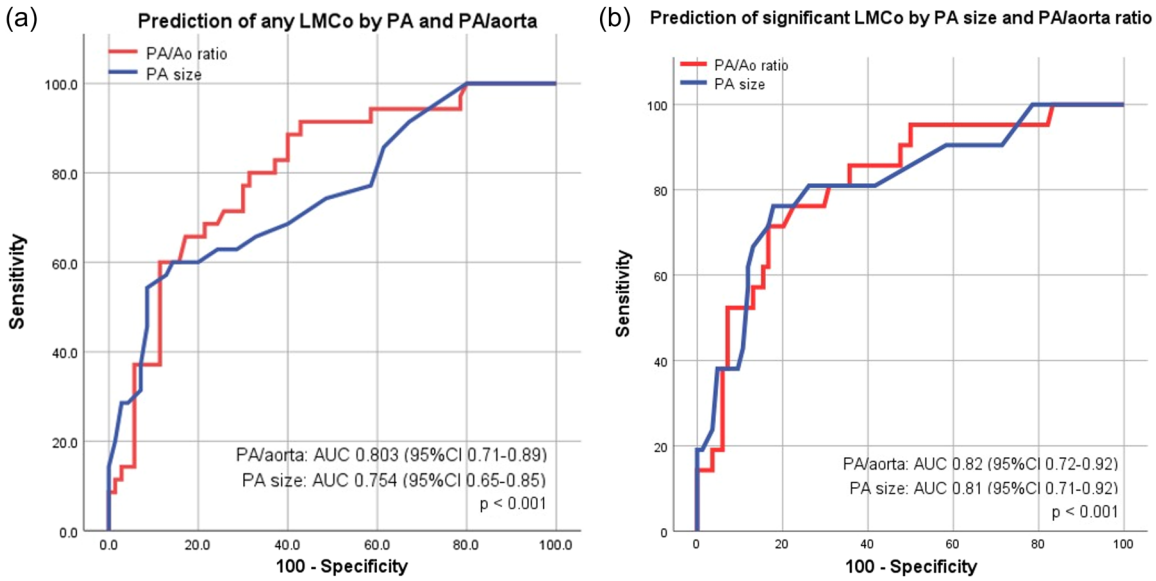


**FIGURE 3** ROC analysis showing predictive factors (main pulmonary artery (PA) size and PA/aorta ratio) for left main coronary artery compression (LMCo) in terms of (a) any degree of LMCo and (b) significant LMCo ≥50%, both $p < 0.001$.

PA/aorta (95% CI 0.72–0.92), both $p < 0.001$ (Figure 3b). The best cut-off values to predict LMCo ≥ 50% were PA size ≥37.5 mm (Sn 81%, Sp 74%) and PA/aorta ≥1.24 (Sn 81%, Sp 69%).

When RV end-diastolic area was added to the prediction model, sensitivity increased to 83% and specificity to 80% for PA size and sensitivity increased to 83% and specificity to 74% for PA/aorta ratio. RV end-diastolic area itself was predictive for significant LMCo ≥ 50% (AUC 0.714, 95%CI 0.57-0.85, p 0.003) with a 31.1 $cm^2$ cut-off (Sn 75%, Sp 55.6%).

## Interventions and outcomes

Twenty-one patients (16.8%) had LMCo ≥ 50% and their individual characteristics and outcomes are outlined in Table 3; one patient with 70% LMCo was lost to follow-up and died, and one patient with severe PH and 80% LMCo presented fatal hemoptysis during cath before revascularization. The remaining patients with LMCo ≥ 50% were discussed for best management. One patient with 60% LMCo had normal instantaneous flow reserve and another patient with 60% LMCo had a large LM (7 mm) and revascularization was withheld.

Nine revascularizations were performed: 7 percutaneous coronary stenting interventions (PCI) (Figure 4), one surgical PEA with coronary artery by-pass grafting (CABG) and one surgical atrial septal defect (ASD) closure and PA plasty. One patient with 30% LMCo had PEA without revascularization and in the control group there were also 3 PEA and 1 ASD closure. The only PCI-related complication was an asymptomatic stent migration into systemic circulation and uneventful deployment of a second stent.

All 4 patients with chest pain reported immediate angina relief after revascularization and sustained clinical improvement (detailed evolution in Table 3). Four follow-up CA were performed: two after PCI (permeable stents) and for both patients who underwent surgical corrections:

- the patient with ASD closure and PA plasty presented first a reduction in LMCo from 80% to 45% and then complete relief of LMCo at 12 months' CA,
- the patient with PEA and CABG had persistent LMCo while having patent grafts at 12 months' CA.

## Survival and event analysis

Population survival was 95% at 1 year, 71% at 3 years, 63% at 5 years and 36% at 10 years. At mean follow-up 3.9 (0.1–17.1) years there were 42 (33.6%) all-cause deaths, of which 38 (90.5%) were CV deaths (30.4% of all patients), 85 (68%) clinical worsening events (defined as lack of improvement after specific therapy, thus either stationary of deteriorating WHO functional class). While not associated with LMCo, the presence of chest pain and pericardial effusion and worse WHO functional class were associated with all-cause and CV death (all $p < 0.05$).

Patients with "any LMCo" and controls had similar survival when considering CV death (p 0.065). Significant LMCo ≥ 50% did not have impact on survival (either all-cause [p 0.255] or CV death [p 0.372]), but it did associate with clinical worsening when compared to no/mild LMCo

**TABLE 3** Data on interventions and outcomes for the 21 patients with significant left main coronary artery compression (LMCo) ≥ 50%.

| case | PH etiology | Chest pain | LMCo (stenosis % and date) | PA size and PA/aorta | Interventions | Outcomes |
|---|---|---|---|---|---|---|
| **#1** | CTEPH | yes | 80% (2022)<br>Previous CA:<br>70% (2019) | 50 mm<br>1.25 | Refuses PEA + CABG.<br>PCI with stent embolisation, second stent with good result | 1.3 y. FU after PCI, angina relief |
| **#2** | iPAH | yes | 80% (2019)<br>Previous CA:<br>60% (2017) | 50 mm<br>1.61 | PCI (Figure 3) | 3.1 y. FU after PCI, angina relief and clinical improvement |
| **#3** | CHD-PAH | no | 60% | 42 mm, 1.40 | IFR = 1, no PCI | 5.6 y. FU, no angina |
| **#4** | CHD-PAH | yes | 80% | 34 mm, 1.31 | Massive hemoptysis during cath and CA, failed therapeutic embolisation attempt | CV death |
| **#5** | CTEPH | no | 85% (2019)<br>Previous CA:<br>0% (2014) | 43 mm<br>1.10 | PEA + CABG 2020<br>Control CA: permeable CABG at 1 y | 3 y FU after surgery, clinical improvement, SV arryhthmia |
| **#6** | CHD-PAH | no | 90% | 38 mm<br>1.09 | PCI<br>Control CA: Permeable stent at 10 y | 12.1 y FU after PCI, no angina |
| **#7** | CHD-PAH | yes | 90% (2006)<br>Previous CA:<br>0% (1998) | 59 mm<br>2.36 | PCI<br>Control CA: Permeable stent at 3 y | recurrent angina at 3 y FU after PCI<br>CV death at 3.9 y |
| **#8** | CHD-PAH | no | 80% | 56 mm<br>1.70 | ASD closure + PA plasty<br>Control CA: no LM stenosis | 1.7 y FU after surgery, no angina |
| **#9** | CTEPH | yes | 60% | 44 mm, 1.38 | PCI | 1 y FU after PCI, no angina, CV death |
| **#10** | CHD-PAH | no | 90% | 44 mm, 1.69 | PCI (Figure 1b) | 1.4 y FU after PCI, no angina |
| **#11** | iPAH | no | 75% (2021)<br>Previous CA:<br>0% (2017) | 44 mm<br>1.45 | PCI | 1.6 y FU after PCI, no angina |
| ***#12*** | CHD-PAH | no | 70% | 41 mm, 1.58 | no | FU no angina, at 4 y CV death |
| ***#13*** | iPAH | no | 80% (2017)<br>Previous CA:<br>0% (2005) | 75 mm<br>2.68 | no | Lost to FU 2007-2017, clinical worsening, no angina, death after 3 y |
| **#14** | CHD-PAH | no | 70% | 50 mm, 1.47 | no | Lost to FU, soon died |
| ***#15*** | CHD-PAH | no | 75% | 30 mm, 1.20 | no | FU 2 y, no angina |
| ***#16*** | CHD-PAH | no | 60% | 44 mm, 1.57 | No | FU 1.6 y, no angina |
| ***#17*** | CHD-PAH | no | 55% | 72 mm<br>2.12 | Large LM diameter (7 mm), no PCI | FU 6.7 y, no angina |
| ***#18*** | CHD-PAH | no | 65% (Figure 1a) | 33 mm, 1.74 | No | FU 3.1 y, no angina |
| ***#19*** | CHD-PAH | no | 50% | 52 mm, 1.58 | No | New enrollment |
| ***#20*** | CTEPH | no | 50% | 52 mm, 1.27 | No | New enrollment |
| ***#21*** | CHD-PAH | no | 55% | 45 mm, 1.67 | No | New enrollment |

Abbreviations: ASD, atrial septal defect; CA, coronary angiography; CABG, coronary artery by-pass grafting; cath., heart catheterization; CHD, congenital heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; CV, cardiovascular; FU, follow-up; IFR, instantaneous flow reserve; iPAH, idiopathic pulmonary arterial hypertension; LM, left main coronary artery; PA, pulmonary artery; PEA, pulmonary thromboendarterectomy; PCI, percutaneous coronary intervention with stenting; PH, pulmonary hypertension; SV, supraventricular; y, years.

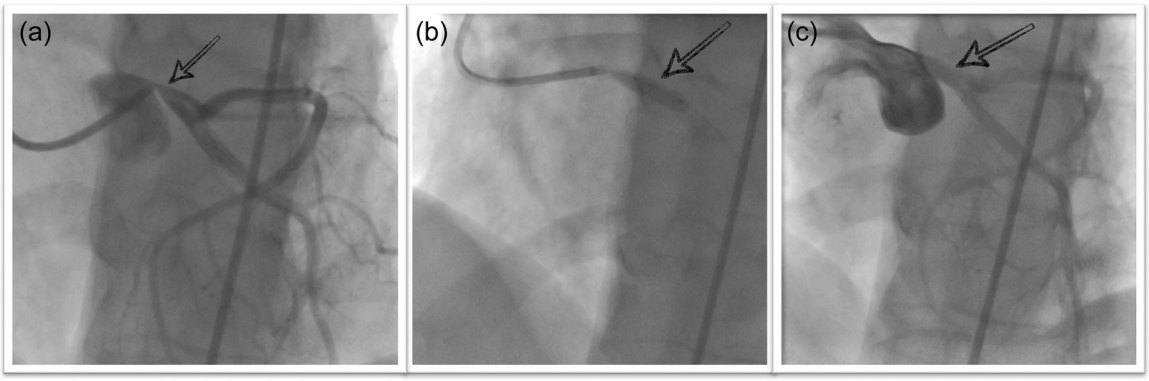


**FIGURE 4** Coronary angiography showing: (a) 80% left main stenosis by extrinsic compression due to the dilated main pulmonary artery; (b) and (c) revascularization procedure during and after percutaneous coronary stent implantation, without procedural complications and with excellent angiographic result.

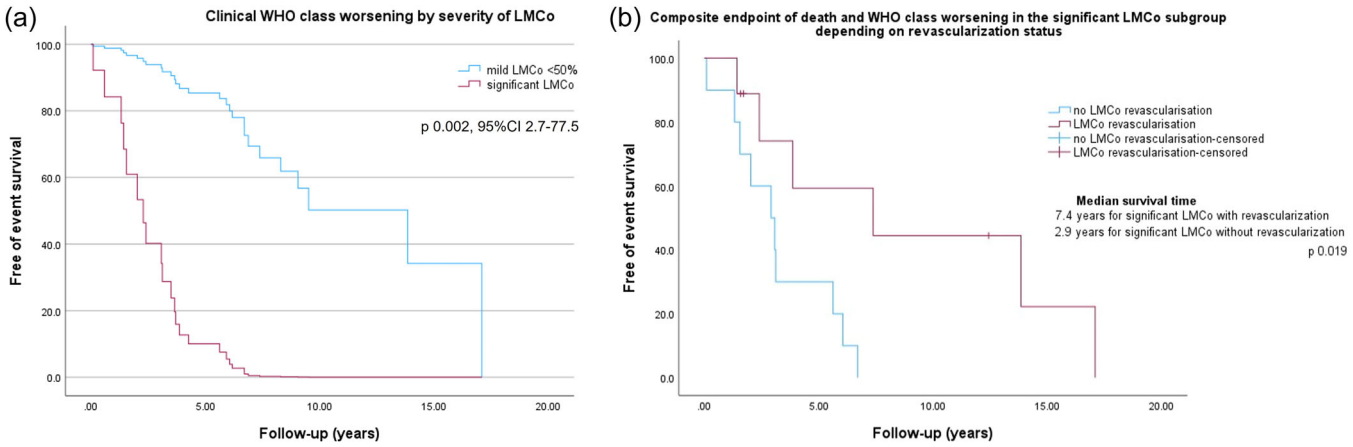


**FIGURE 5** Longitudinal event analysis showing that (a) patients with significant left main coronary artery compression (LMCo) ≥ 50% presented clinical worsening when compared to patients with LMCo < 50% (p 0.002) and (b) patients with significant left main coronary artery compression (LMCo) ≥ 50% without revascularization had clinical worsening and worse survival at the composite end-point than the patients without revascularization (p 0.019).

(p 0.002) (Figure 5a). Patients with significant LMCo ≥ 50% without revascularization (n, 12; 57.1%) had worse prognosis when considering the composite endpoint of CV death/clinical deterioration at univariable regression analysis, with a median survival time of 2.9 years, mean 3.2 years (95% CI 1.9–4.6) compared to the revascularization subgroup (n, 9; 42.8%) who had median survival time 7.4 years, mean 9.05 years (95% CI 4.1–13.9) (p 0.019) (Figure 5b).

## DISCUSSION

### LMCo characteristics, associations, and predictors

Significant original research on the topic other than case reports is exceptional because while some suggest reasonable associations, they do not actually provide valid data on prevalence, associations and outcomes of LMCo in precapillary PH.

*Kajita* et al reported the first relevant case series in 2001, including seven adult patients with LMCo≥50% (1 iPAH, others CHD) without data on prevalence, associations or predictors for LMCo.[7] In 2004 *Mesquita* et al published another 7 LMCo ≥ 50% (iPAH or CHD) and was the first to provide statistical analysis, but the small number of cases (total, 36) is a major limitation in estimating prevalence and confidence (associations found between LMCo and PA, PA/aorta and lack of associations between LMCo and: sex, age, PH etiology, angina and mPAP).[11] Another small study with 8 LMCo (1 CTEPH, others PAH) out of 23 CA by *Velázquez Martín* et al found no associations were found between LMCo and: angina, PA or PA/aorta, PA pressures, PH type or duration, age, sex, WHO class, 6MWT.[6]

The papers by *Lee* et al and *Akbal* et al have controversial value, the first being unclear on LMCo status (no invasive confirmation at CA) and without specific data on PH type, interventions/outcomes and the second having mixed PH population including 49 (18.2%) patients with PH associated to lung diseases and left heart diseases, which confuses relevance in PAH.[12,13] *Nuche Berenguer* et al found 10 LMCo out of 86 patients with PA aneurysm at CT (9 underwent PCI, 1 PA plasty), only reporting on PA-LMCo association no other information (not either PH type).[17]

Ultimately, the only solid original research on LMCo in PAH is that by *Galiè* et al, which also has an overlapping follow-up study by *Saia* et al.[4,5] The former reported 48 LMCo≥50% confirmed at CA out of 121 patients with group 1 PAH, chest pain and suggestive LMCo at CT, estimating LMCo≥50% prevalence at 40% of patients with chest pain. PA and aorta sizes were reported at CT. Associations were found between LMCo and PA absolute and index size, PA/aorta, and LMCo≥50% was predicted by PA size (≥40 mm had Sn 83% and Sp 70%, AUC 0.8512), PA index size (24 mm/m$^2$ had Sn 79% and Sp 68%, with AUC 0.8472) and PA/aorta (≥1.5 had Sn 73% and Sp 70%, AUC 0.8007).[4]

The present study focused on LMCo and analyzed the most heterogenous precapillary PH population (including group 4, CTEPH and group 5 with PA wedge pressure ≤15 mmHg). In lack of recommendations, CA was performed considering chest pain, PA aneurysm, left ventricular dysfunction, CV risk factors and before planned surgery. This screening strategy differs from previous studies which considered only patients with chest pain or PA aneurysm.[4,6,14,17] Having less restrictive CA indications in a large and more heterogenous PH population this study provides a good estimation of LMCo ≥ 50% prevalence in precapillary PH of 16.8%.

LMCo was not associated with PH type in *Galiè* et al and *Mesquita* et al's research, but our recent meta-analysis pooled data on the topic and revealed an association between LMCo and CHD-PH (61.5% of all LMCo cases, 66.6% of LMCo ≥ 50%). In this context our analysis is to our knowledge the first single-center research that shows conclusive association between LMCo and CHD-PH. This might explain our novel findings regarding the association between LMCo and Qp/Qs and LMCo ≥ 50% and higher $SvO_2$.

In line with previous studies, LMCo was predicted by PA size, PA/aorta ratio.[3,11,12,14–16] The novel finding is the added value of RV end-diastolic area to PA size and PA/aorta to better predict LMCo. In contrast to previous suggestions we did not find significant associations between LMCo and chest pain, sex, age, body conformation, PH duration, PA pressures or PVR.[6,11,14–16]

Our imaging data was obtained at echocardiography making it the largest series on the topic. The results are similar to studies that associated LMCo with PA size and PA/aorta size at CT, finding that may validate ultrasonographic evaluation as non-inferior for LMCo screening.[4,5,17] This is an important observation because low cost, wide availability and fewer risks are clear promoters of echocardiography in real-life PH cohorts.

## LMCo interventions and long-term outcomes

Few case-control studies provide longitudinal data: *Velázquez Martín* et al (8 PCI, median follow-up 20 months, three events at survival analysis), *Galiè* et al (45 PCI and 3 PA reconstructions, mean follow-up 22 ± 13 months, five restenoses at 9 months' routine control CA with repeat revascularization, death or lung transplant was 5%, composite endpoint death/transplant/restenosis was 30% at 36 months) and *Saia* et al (reports on the same cohort, extended mean follow-up 4.5 ± 1.8 years, 5 (9.4%) stent misplacements, 19 (37.3%) deaths (14 (27.5%) cardiac) with similar survival distribution between groups, but control group is not described (p 0.814)).[4–6]

The present study provides one of the longest follow-up data excepting *Saia* et al.[4,5,17] This is the first study to find an independent association between "any LMCo" and WHO functional class and a possible association between LMCo≥50% and lower BNP values at enrollment. The latter association was not explained by WHO functional class distribution, and should be interpreted cautionarily as it did not remain significant when adjusting for WHO class. More importantly, there was a significant association between LMCo ≥ 50% and clinical deterioration at long-term follow-up. Moreover, the lack of revascularization in LMCo ≥ 50% significantly correlated with worse CV survival and clinical deterioration, this being, to our knowledge, the first analysis of significant LMCo with versus without revascularization.

Revascularization was performed after Heart Team discussion for best management considering the clinical status, degree of LMCo and LM size, lack of specific recommendations (extrapolating from atheromatous LM stenosis) and controversial data on outcomes in the early years, given the fact that LMCo has the advantage of being more amenable to PCI when compared to LM stenosis by aterosclerosis (which may require more complex revascularization techniques) and unprotected stenting recently yields good results.[18]

The single periprocedural complication was stent migration in one case, so we consider that LMCo may be performed safely. At follow-up no stent-related

complications were found. Angina relief occurred immediately in the four symptomatic patients, there was 1 case of recurrent chest pain at long-term (3 years) but with permeable stent. The remaining patients with revascularization had no angina at any time.

Of note, 4 patients with previously normal CA developed LMCo and one 60% LMCo progressed to 80% during follow-up, requiring PCI. Active screening for LMCo is therefore important in high-risk patients and recommendations are needed to prevent an excess of morbi-mortality. Studies for predictive parameters of LMCo are essential for best management given that ischemia testing has a limited role in LMCo detection in a population with limited exercise tolerance, abnormal baseline ECG and with generally contraindicated stress tests if suspected LM stenosis.[3,14,18–20]

## Study limitations

Heterogenity is an advantage but also a drawback of this study. While it shows a good estimate for real-life LMCo prevalence and predictors, CA was at clinician's indication and so were supplemental coronary function tests and the revascularization strategy. The latter also depended on patients' choice. These were sources of bias we couldn't adjust for. While patients underwent complete PH workup at enrollment, chest CT was not readily available for PA systematic monitoring. The relative small number of patients in this cohort is another limitation but it reflects the real-life prevalence of these rare entities.

## Conclusions

In a heterogenous precapillary PH cohort, the prevalence of LMCo was fairly high and was associated to CHD-PH. The best predictors of LMCo were PA size and PA/aorta, with increased predictive value when adding RV end-diastolic area to the prediction model. Significant LMCo (≥50%) was associated with clinical worsening and patients with untreated LMCo ≥50% had a worse prognosis (clinical deterioration and worse survival rates) compared to patients who underwent revascularization. Revascularization procedures were performed safely and with good outcomes (angina relief, clinical improvement and increased survival).

### AUTHOR CONTRIBUTIONS

All authors have contributed to the paper. Dr. Roxana Enache is the guarantor.

### ACKNOWLEDGMENTS

Dr. Ruxandra Badea (ruxandra.badea@drd.umfcd.ro) and Dr. Roxana Enache (roxenache@gmail.com) contributed equally to the document and are joint first authors. Publication of this paper was supported by the University of Medicine and Pharmacy Carol Davila, through the institutional program Publish not Perish.

### DATA AVAILABILITY STATEMENT

Data available on request from the authors.

### ETHICS APPROVAL

Patient informed consent forms have been obtained and the research in this paper corresponded to institutional requirements.

### ORCID

*Ruxandra Badea* http://orcid.org/0000-0003-3807-1384

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**How to cite this article:** Badea R, Enache R, Predescu LM, Platon P, Catana N, Deleanu D, Iosifescu AG, Radu N, Radu T, Olaru-Lego G, Coman IM, Popescu BA. Left main coronary artery compression in precapillary pulmonary hypertension. Pulm Circ. 2024;14:e12391. https://doi.org/10.1002/pul2.12391