Pulmonary Edema Following Initiation of Parenteral Prostacyclin Therapy for Pulmonary Arterial Hypertension

A Retrospective Study

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BACKGROUND: Pulmonary edema may complicate the use of pulmonary arterial hypertension (PAH)-targeted therapies. We aimed to determine the proportion of patients who develop pulmonary edema after initiation of parenteral prostacyclin therapy, to identify its risk factors, and to assess its implications for hospital length of stay and mortality.

METHODS: A retrospective cohort study of patients with PAH at the initiation of parenteral prostacyclin between 1997 and 2015 enrolled in the Cleveland Clinic PAH registry. Pulmonary edema was defined as at least one symptom or clinical sign and radiographic evidence of pulmonary edema. We determined patient characteristics predictive of pulmonary edema as well as the association between pulmonary edema and hospital length of stay (LOS) and 6-month mortality.

RESULTS: One hundred and fifty-five patients were included (median age, 51 years; female, 72%; white, 85%; idiopathic, 64%; and connective tissue disease [CTD], 23%). Pulmonary edema developed in 33 of 155 patients (21%). Independent predictors of pulmonary edema were high right atrial pressure (RAP), CTD etiology, and the presence of three or more risk factors for left heart disease (LHD). Pulmonary edema was associated with a 4.5-day increase in hospital LOS (95% CI, 1.4-7.5 days; $P < .001$) and a 4-fold increase in 6-month mortality (OR, 4.3; 95% CI, 1.28-14.36; $P = .031$).

CONCLUSIONS: Pulmonary edema occurred in 21% of patients with PAH initiated on parenteral prostacyclin. Three or more risk factors for LHD, CTD-PAH, and a high baseline RAP were independent predictors of pulmonary edema. Pulmonary edema was associated with a prolonged hospital LOS and increased 6-month mortality.

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KEY WORDS: prostacyclin; pulmonary arterial hypertension; pulmonary edema

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ABBREVIATIONS: CTD-PAH = connective tissue disease-associated pulmonary arterial hypertension; DLCO = diffusion capacity of the lung for carbon monoxide; IQR = interquartile range; LHD = left heart disease; LOS = length of stay; LV = left ventricular; PAH = pulmonary arterial hypertension; PCH = pulmonary capillary hemangiomatosis; PVOD = pulmonary venoocclusive disease; RAP = right atrial pressure

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Parenteral prostacyclin therapy is currently recommended for patients with high-risk pulmonary arterial hypertension (PAH),¹ but it can be complicated by the development of pulmonary edema. It is well recognized that PAH-targeted therapies may unmask pulmonary venoocclusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH) by causing pulmonary edema.²⁻⁵ However, registries have also shown that a large proportion of patients with PAH have cardiovascular risk factors for left heart disease (LHD),⁶ and LHD has been described in patients diagnosed with PAH and a resting pulmonary artery wedge pressure ≤ 15 mm Hg, particularly in systemic sclerosis.⁷⁻⁹

Materials and Methods

We retrospectively examined a cohort of adult patients enrolled in the Cleveland Clinic Pulmonary Hypertension Registry (IRB 8097) with a diagnosis of group 1 PAH, and who were initiated on parenteral prostacyclin therapy between 1997 and 2015. These patients were diagnosed and categorized as group 1 PAH as adjudicated by a group of pulmonary hypertension specialists.

The primary outcome of the study was the development of pulmonary edema within 7 days of initiation of parenteral prostacyclin therapy. Secondary outcomes were duration of ICU and hospital stay, mortality in the hospital and at 3 and 6 months, as well as long-term transplant-free survival. We defined pulmonary edema as the presence of at least one new symptom (new or worsening dyspnea, orthopnea) or sign (new or worsening rales on pulmonary examination) of pulmonary edema and evidence of new or worsening pulmonary edema on chest radiography.¹⁰⁻¹² Chest radiograph signs of pulmonary edema were defined as at least one or more of the following: Kerley B lines, interstitial reticular opacities, vascular cephalization, alveolar infiltrates, or pleural effusions.¹⁰⁻¹⁴

The type of prostacyclin analog, the initiation dates, and doses were extracted and progress notes were meticulously scrutinized to determine the subjective and physical examination findings of pulmonary edema. Chest radiography results documented by

The frequency of pulmonary edema in patients with PAH started on parenteral prostacyclin therapy is not known. It is also uncertain whether the development of pulmonary edema in PAH has any short- or long-term complications. Besides a pretreatment suspicion of PVOD/PCH, there are no known risk factors for the development of pulmonary edema.

We hypothesized that the proportion of patients developing pulmonary edema after initiation of prostacyclin analogs is higher than expected due to LHD and/or unrecognized PVOD/PCH. We aimed to identify risk factors predisposing toward development of pulmonary edema, and to assess its effect on outcomes including hospital length of stay (LOS) and mortality.

radiologists were reviewed to ascertain the presence of pulmonary edema. Factors associated with LHD were extracted in order to determine the cardiovascular profile of the patients. As per the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) study, risk factors for LHD were defined as three or more of the following: history of coronary artery disease, diabetes mellitus, systemic hypertension, BMI ≥ 30 , and atrial fibrillation.¹⁵

Statistical Analysis

Continuous data are presented using medians (interquartile range [IQR]) and categorical data as counts (%). We calculated the proportion of patients developing pulmonary edema and a 95% confidence interval for this estimate, using the Wald test. Comparisons between groups were done using Wilcoxon and χ^2 tests, when appropriate. Multiple logistic regression was performed to determine predictors of pulmonary edema (OR for the interquartile range effect for all continuous predictors). Multiple imputation was done for any missing values in predictors, using additive regression bootstrapping and predictive mean matching. Univariate logistic regression was used for 3- and 6-month mortality. Long-term survival was assessed with Kaplan-Meier curves and by log-rank test and Cox proportional hazard modeling. Statistical analysis was performed with the statistical package R, version 1.0.44 (R Foundation).

Results

Study Population

From a total of 224 patients with group 1 PAH newly started on parenteral prostacyclin, we included 155 patients (Fig 1). The predominant reason for exclusion was inability to ascertain development of pulmonary edema due to incomplete records or missing data, mostly secondary to conflicting or missing documentation of doses and timing of initiation of parenteral prostacyclin therapy.

Table 1 shows the baseline characteristics of the cohort. The majority of the study subjects were female (81.9%)

with a median age of 51 (39-57) years and white (85%). The etiology of PAH was mostly idiopathic at 64%. While left ventricular systolic function was normal, approximately one-half of the patients had grade I diastolic dysfunction on echocardiography. The majority of patients (152 of 155) did not have moderate or severe left heart valvular abnormalities on echocardiography. One patient had moderate mitral stenosis with a pulmonary capillary wedge pressure of 11 mm Hg and developed pulmonary edema. Two subjects had moderate mitral regurgitation, none of whom developed pulmonary edema. Hemodynamics were severely compromised with a median right atrial pressure (RAP)

Figure 1 – Flow diagram of study population.

of 12 mm Hg (IQR, 7-17), mean pulmonary artery pressure of 55 mm Hg (IQR, 47-63), pulmonary capillary wedge pressure of 11 mm Hg (IQR, 8-16), and low cardiac index of 1.9 L/min/m² (IQR, 1.6-2.4). The most common prostacyclin analog used was intravenous epoprostenol (86%), followed by intravenous treprostinil (11.6%) and subcutaneous treprostinil (2%).

Frequency and Risk Factors for Pulmonary Edema

Thirty-three of 155 patients (21.3%; 95% CI, 15.6%-28.7%) developed pulmonary edema after initiation of prostacyclin analog. The specific radiographic findings in the 33 patients who developed pulmonary edema are shown in Table 2. The median time from prostacyclin initiation to pulmonary edema detection was 2 days (IQR, 1-4 days). Of the 33 who developed pulmonary edema, 28 were receiving intravenous epoprostenol with a median discharge dose of 8 ng/kg/min (IQR, 6-9) and five were receiving intravenous treprostinil with a median discharge dose of 9 ng/kg/min (IQR, 9-25).

Table 1 presents the baseline characteristics of subjects who did and did not develop pulmonary edema. There was no significant difference in age, sex, or race.

Connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) was more prevalent in those who developed pulmonary edema (39.4% vs 18.9%; $P = .045$), while baseline FVC percent predicted (80% vs 74%) and diffusion capacity of the lung for carbon monoxide percent predicted (DLCO) (63% vs 46%) were lower ($P = .044$ and 0.032 , respectively). Severe DLCO impairment of $< 55\%$ was higher in the group that developed pulmonary edema (68% vs 37.7%; $P = .01$). The pulmonary edema cohort also had a higher RAP (17 vs 10 mm Hg; $P = .005$) and a trend toward a lower cardiac index. The presence of

three or more LHD risk factors was higher in the pulmonary edema group as well (18% vs 5%; $P = .031$). Eight of the 33 subjects who developed pulmonary edema underwent pulmonary vasoreactivity testing with inhaled nitric oxide or intravenous epoprostenol. None of them had positive results on vasoreactivity testing, and none developed pulmonary edema during the testing.

On multivariate logistic regression analysis, CTD-PAH, higher baseline RAP, and the presence of three or more LHD risk factors were independent predictors of the development of pulmonary edema (Table 3). CTD-PAH was associated with a greater than 3-fold increase in the risk of pulmonary edema, and a baseline RAP of 17 mm Hg compared with 7 mm Hg was associated with an almost threefold increased risk. The presence of three or more LHD risk factors was associated with a 4.4-fold increased risk of pulmonary edema.

Impact of Pulmonary Edema on Clinical Outcomes

Eight of the 33 patients with pulmonary edema (24%) required deescalation or discontinuation of prostacyclin analog therapy and two (6%) required invasive mechanical ventilation. Pulmonary edema was associated with a mean increase of 4.5 days (95% CI, 1.4-7.5; $P < .001$) in hospital LOS. Development of pulmonary edema was associated with a more than fourfold increase in 6-month mortality (OR, 4.3; 95% CI, 1.28-14.36; $P = .031$) (Table 4).

After a median follow-up of 46 months (IQR, 13-101 months), pulmonary edema was associated with a 1.5-fold increased risk of death or lung transplantation (hazard ratio, 1.54; 95% CI, 0.97-2.36; $P = .06$). Twelve- and 36-month transplant-free survival were 67% and 40%, respectively, in those who developed pulmonary edema, compared with 81% and 65% among patients who did not develop pulmonary edema (log-rank $P = .051$) (Fig 2).

Of the 32 patients who developed pulmonary edema and survived the index hospitalization, 27 survived at 6 months (84.4%), of whom 24 had a follow-up chest radiograph at our center a median of 4.1 months after discharge (IQR, 2.2-6.1 months). Six of those 24 (25%) had persistent radiographic evidence of pulmonary edema, while 18 (75%) had complete resolution. In two of the 27 patients (7.4%) alive at 6 months, parenteral prostacyclin therapy was discontinued. In the remaining 21 patients with available data the median dose of IV epoprostenol ($n = 18$) was 20 ng/kg/min (13.9-30.7) and

TABLE 1] Baseline Characteristics and Comparison of Patients by Development of Pulmonary Edema

Characteristic	Overall (N = 155)	No Pulmonary Edema (n = 122)	Pulmonary Edema (n = 33)	P Value
Age, y	51 (39-57)	49 (39-56)	54 (43-60)	.111
Male sex	28 (18.1%)	25 (20.5%)	3 (9.1%)	.209
White	132 (85.2%)	103 (84.4%)	29 (87.9%)	.827
BMI, kg/m ²	27 (23-33)	27 (22-33)	29 (25-32)	.472
PH subtype				.045
IPAH	99 (63.9%)	82 (67.2%)	17 (51.5%)	
CTD-PAH	36 (23.2%)	23 (18.9%)	13 (39.4%)	
Other	20 (12.9%)	17 (13.9%)	3 (9.1%)	
DM	23 (15.4%)	16 (13.8%)	7 (21.2%)	.376
CAD	13 (8.3%)	9 (7.4%)	4 (12.1%)	.604
HTN	62 (41.9%)	46 (40%)	16 (48.5%)	.502
Atrial fibrillation	8 (5.2%)	6 (5.0%)	2 (6.0%)	
FVC % predicted	79 (66-89)	80 (68-90) (n = 101)	74 (62-80) (n = 24)	.044
DLco % predicted	58 (41-73)	63 (42-74) (n = 90)	46 (35-59) (n = 22)	.032
DLco < 55 % predicted	49 (43.7%)	34 (37.7%) (n = 90)	15 (68.1%) (n = 22)	.01
LV ejection fraction, %	55 (55-60)	55 (55-60)	55 (55-60)	.201
LV diastolic dysfunction	77 (50.7%)	62 (52.1%)	15 (45.5%)	.632
RAP, mm Hg	12 (7-17)	10 (7-16)	17 (8-19)	.005
mPAP, mm Hg	55 (47-63)	55 (46-62)	60 (49-69)	.103
PAWP, mm Hg	11 (8-16)	10 (8-16)	12 (9-16)	.31
CI, L/min/m ²	1.9 (1.6-2.4)	2 (1.6-2.4)	1.7 (1.5-2.0)	.054
PVR, Wood units	12 (8-16)	11 (9-15)	13 (9-18)	.061
LA diameter, cm	3.61 (0.67)	3.63 (± 0.66)	3.56 (0.74)	.649
LA size				.146
Normal	127 (84.7%)	98 (83.8%)	29 (87.9%)	
Mild enlargement	16 (10.7%)	13 (11.1%)	3 (9.1%)	
Moderate enlargement	6 (4.0%)	6 (5.1%)	0 (0.0%)	
Severe enlargement	1 (0.7%)	0 (0.0%)	1 (3.0%)	
LHD risk factors ≥ 3	12 (7.7%)	6 (4.9%)	6 (18.2%)	.031

Data are presented as No. (%) and median (25th-75th percentile). CAD = coronary artery disease; CI = cardiac index; CTD-PAH = connective tissue disease-associated pulmonary arterial hypertension; DLco = diffusion capacity of lung for carbon monoxide; DM = diabetes mellitus; HTN = hypertension; IPAH = idiopathic pulmonary arterial hypertension; LA = left atrial; LHD = left heart disease; LV = left ventricular; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RAP = right atrial pressure.

treprostinil (n = 3) was 15 ng/kg/min (12-38). Among 116 survivors without pulmonary edema, four patients (3.4%) discontinued parenteral prostacyclin at 6 months. For the remaining patients, the median dose of epoprostenol was 16 ng/kg/min (10-25 ng/kg/min; n = 81) and for treprostinil it was 23 ng/kg/min (15-37.2 ng/kg/min; n = 10).

Discussion

Pulmonary edema occurred in 21% of patients with group 1 PAH after the initiation of parenteral prostacyclin therapy. Three or more risk factors for

LHD, CTD-PAH, and a high baseline RAP were independent predictors of pulmonary edema. The development of pulmonary edema was associated with a prolonged hospital LOS and increased 6-month mortality. These results are in line with emerging evidence of LHD⁸ and venule involvement in PAH.^{16,17} Severe right ventricular dysfunction, perhaps leading to left ventricular (LV) impairment, could play a role as well.

The strong association of LHD risk factors and development of pulmonary edema suggests that LHD may have played a role despite the similar left atrial size

TABLE 2] Chest Radiograph Features in Patients Who Developed Pulmonary Edema^a

Radiographic Features of Pulmonary Edema	Percentage (n = 33)
Interstitial reticular opacities	13 (39%)
Vascular cephalization	8 (24%)
Alveolar infiltrates	8 (24%)
Pleural effusion	18 (54%)

^aSome patients had more than one radiographic sign.

of the two groups. LHD is often underdiagnosed in patients with PAH, particularly in association with systemic sclerosis,^{7,18} which is in keeping with the high prevalence of myocardial fibrosis in this population.¹⁸⁻²³ This builds the case for considering fluid challenge in patients with PAH to screen for LHD as suggested by Robbins et al.⁸ Similarly, these investigators noted left atrial enlargement, older age, history of hypertension, and BMI to be predictors of pulmonary venous hypertension.⁸

Higher baseline RAP was another independent predictor of pulmonary edema. This suggests that baseline fluid overload and more severe right ventricular failure could contribute to the development of pulmonary edema. We speculate that worse right ventricular function, as suggested by higher RAP, led to LV diastolic impairment through ventricular interdependence, which has been suggested by multiple other studies.²⁴⁻³⁰ In severe cases,

TABLE 3] Predictors of Pulmonary Edema in a Multivariable Logistic Regression Model

Characteristic	OR	95% CI	P Value
Age	1.01		NS
Male sex	0.48		NS
White	3.1		NS
CTD-PAH vs IPAH	3.15	0.95-10.41	.06
FVC % predicted	0.99		NS
D _l CO % predicted	0.99		NS
LVEF	1.03		NS
LV diastolic dysfunction	0.58		NS
RAP ^a	2.75	1.17-6.43	.02
mPAP	1.0		NS
PAWP	1.04		NS
CI	2.3		NS
PVR	1.17		NS
LHD risk factors ≥ 3	4.41	1.02-19.07	.046

LVEF = left ventricular ejection fraction; NS = not significant. See Table 1 legend for expansion of other abbreviations.

^aOR is for the comparison of RAP of 17 vs 7 mm Hg.

a “deconditioned” LV may not be able to accommodate increased pulmonary blood flow after initiation of prostacyclin therapy. PAH-targeted therapies are known to cause pulmonary edema in PVOD and PCH,^{4,5} albeit in the absence of incidence data.^{3,4,31} PVOD and PCH are rare forms of pulmonary hypertension, representing 0.4% of cases in a large pulmonary hypertension registry.⁶ However, it is important to recognize PVOD/PCH, as the use of PAH-targeted therapies in patients with unrecognized PVOD/PCH can be complicated by fatal pulmonary edema.⁴ Furthermore, a heritable form caused by *EIF2AK4* mutations with an autosomal recessive inheritance pattern has been described in PVOD³² and PCH.³³ Interestingly, pathogenic biallelic *EIF2AK4* mutations are found rarely in patients diagnosed clinically with PAH.^{34,35} While PVOD and PCH are clinically and genetically unique, previous studies suggest histopathologic and biologic similarities among patients diagnosed with PAH and PVOD/PCH.^{36,37} Luminal fibrosis of postcapillary venules has been observed in PAH associated with CTD.¹⁶ Low D_lCO and the presence of septal lines, centrilobular nodules, and lymphadenopathy on chest CT scanning are suggestive of PVOD/PCH,^{3,38,39} although these findings are not specific. In our study, patients who developed pulmonary edema were more likely to have CTD-associated PAH and had lower FVC and D_lCO. These findings suggest postcapillary pulmonary hypertension in cases of pulmonary edema. Only eight of the 33 patients who developed pulmonary edema had baseline chest CT scans available for review. Three of the eight subjects met none or one of the criteria, while five subjects met two or three CT scanning criteria for PVOD. Our chest CT scan data, albeit limited, suggest the presence of postcapillary pulmonary hypertension.

Regardless of the mechanism, the development of pulmonary edema is associated with poor outcomes including prolonged hospitalizations and increased 3-month, 6-month, and long-term mortality. Given the implications of poor outcomes in these patients, there should be a higher suspicion for pulmonary venous involvement amongst patients diagnosed with group 1 PAH. We recommend a thorough evaluation to identify suspected PVOD/PCH and/or significant LHD before initiating parenteral prostanoids, and careful monitoring for pulmonary edema whenever parenteral prostanoids are initiated.

There are certain limitations to this study. As this is a retrospective cohort study, we cannot calculate a true incidence of pulmonary edema. We had to exclude 47 of

TABLE 4] Survival at Discharge and at 1, 3, and 6 Months by Development of Pulmonary Edema

Outcome	Overall	No Pulmonary Edema	Pulmonary Edema	P Value
	(N = 155)	(n = 122)	(n = 33)	
Alive at discharge	154 (99.4%)	122 (100%)	32 (97%)	.482
PGI ₂ dose at discharge				
Epoprostenol	6 (5-8)	6 (5-8) (n = 106)	8 (5-9) (n = 27)	.07
Treprostinil	15 (9-18.5)	15.5 (10.5-18) (n = 16)	9 (8-28.5) (n = 5)	.87
Alive at 1 mo	152 (98.1%)	122 (100%)	30 (90.9%)	.008
Alive at 3 mo	150 (96.8%)	121 (99.2%)	29 (87.9%)	.007
Alive at 6 mo	143 (92.3%)	116 (95.1%)	27 (81.8%)	.031
ICU LOS	3 (2-4)	3 (2-4)	4 (2-6)	.108
Hospital LOS	6 (4-8)	5 (4-8)	8 (5-14)	.001

Data are presented as count (%) and median (25th-75th percentile). LOS = length of stay; PGI₂ = prostacyclin analog.

224 eligible patients because of missing data that did not allow for the ascertainment of pulmonary edema. Very few patients had chest CT images for review. While we used a rigorous definition for pulmonary edema, the symptoms and radiologic signs are not specific, and we cannot rule out some misclassification. For example, pleural effusions can occur in PAH due to right heart failure.^{40,41} Four of the 33 patients with pulmonary edema had received that diagnosis based solely on new or worsening pleural effusions. Reclassifying those four subjects, the rate of pulmonary edema was 29 of 155 patients (18.7%; 95% CI, 13.4%-25.6%). We performed a sensitivity analysis using this revised definition of pulmonary edema (see [e-Appendix 1](#), [e-Tables 1-3](#)). The

main results were not different in this sensitivity analysis. Furthermore, as defined, pulmonary edema was associated with important clinical outcomes such as hospital length of stay and mortality. Last, this study was conducted at a single center, and the observations may not be generalizable to other settings.

Conclusion

The development of pulmonary edema in one in five patients started on parenteral prostacyclin therapy suggests that postcapillary involvement is more prevalent than widely believed. LHD and PVOD/PCH are important considerations, and each has prognostic and treatment implications.

Figure 2 – Transplant-free survival according to development of pulmonary edema. Twelve- and 36-month transplant-free survival were 67% and 40%, respectively, in those who developed pulmonary edema, compared with 81% and 65% in patients who did not develop pulmonary edema at baseline.

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Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

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