Severe PH-ILD presenting as RV failure: stabilisation with intravenous prostacyclin and maintenance with inhaled prostacyclin

R. Parikh, A. Thomas, A. Sharofi, N. Moallem, G. Fiscus, H. W. Farber


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Cover Letter:

To the Editor,

Pulmonary hypertension (PH) related to interstitial lung disease (ILD) carries significant morbidity and mortality. The results of the INCREASE trial have shown the importance of identifying these PH-ILD patients early in their disease course to initiate inhaled prostacyclin therapy and timing of referral for lung transplant. However, patients with PH-ILD may develop right ventricular (RV) failure; in this case, advanced treatment with intravenous prostacyclins may be warranted. In this study, we introduce the concept of induction and maintenance therapy for PH-ILD with concomitant RV failure. This manuscript highlights the potential of utilizing intravenous prostacyclin to stabilize RV function during an induction phase of treatment followed by subsequent maintenance treatment with inhaled prostacyclin.

Sincerely,

Raj Parikh and co-authors
Title: Severe PH-ILD presenting as RV failure: stabilization with intravenous prostacyclin and maintenance with inhaled prostacyclin

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Abbreviation List:
Abstract:

**Background:** Pulmonary hypertension (PH) worsens the morbidity and mortality in interstitial lung disease (ILD). While the INCREASE trial highlighted the use of inhaled prostacyclin in PH-ILD patients, such therapy may be inadequate when right ventricular failure (RVF) is also present. In this study, we report use of intravenous prostacyclin in three PH-ILD patients to stabilize RV function followed by transition to maintenance inhaled prostacyclin therapy.

**Methods:** We evaluated three consecutive PH-ILD patients with RVF. RV afterload and pulmonary vascular resistance (PVR) were treated with intravenous prostacyclin during the induction phase of therapy. Patients transitioned from intravenous prostacyclin to maintenance phase of treatment with inhaled prostacyclin once three transition criteria were met: cardiac index (CI) >2 L/min/m², PVR <7 Wood-units (WU), and tricuspid annular planer systolic excursion (TAPSE) change >1mm or TAPSE >1.6cm.

**Results:** Pre-treatment parameters for the three patients were mean PVR of 14.3 WU, mean Fick CI of 1.8 L/min/m², and mean TAPSE of 1.4cm. The average intravenous prostacyclin dose at time of transition to maintenance therapy was 20.7 ng/kg/m² of treprostinil. At 3-month follow-up, the mean PVR was 6.3 WU, Fick CI 2.2 L/min/m², and TAPSE 1.7cm.

**Conclusion:** This case series of three PH-ILD patients with RVF introduces the concept of induction phase of intravenous prostacyclin initiation followed by transition to maintenance inhaled prostacyclin therapy. Further development of this treatment algorithm with refinement of the transition criteria, potential testing in a clinical trial, and longer-term follow-up is warranted to improve the outcomes of advanced PH-ILD patients with concomitant RVF.

Abstract word count: 250
1. Background

Pulmonary hypertension (PH) worsens the prognosis of interstitial lung disease (ILD) resulting in deteriorating functional status, increasing need for supplemental oxygen, and leading to poorer outcomes.\(^1\)\(^-\)\(^5\) The prevalence of PH increases with progression of lung disease; more than 60% of end-stage ILD may have concomitant PH.\(^6\)\(^-\)\(^9\)

The clinical utility of PH-specific therapy in PH-ILD patients was demonstrated by the INCREASE trial in which treatment with inhaled treprostinil showed improvement in 6-minute walk distance (6MWD).\(^10\)\(^-\)\(^11\) However, many ILD patients present with PH more severe than those enrolled in the INCREASE trial. As such, two issues arise: 1) how to suspect and diagnose PH earlier in the course of the disease; and 2) what to do in those patients who present in right ventricular failure (RVF). The first issue can be addressed by the recently developed PH-ILD Detection tool.\(^12\)

The second issue is somewhat more difficult in that RVF can further complicate the management similar to what occurs in decompensated World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH).\(^12\)\(^-\)\(^16\) In such patients, advanced prostacyclin therapy may be considered such as with intravenous treprostinil or epoprostenol.\(^13\)\(^-\)\(^14\) While advanced prostacyclins have well-established benefits in WHO Group 1 PAH, similar results are not clear in PH-ILD because such treatment has the potential to worsen hypoxemia by causing ventilation/perfusion (VQ) mismatch in the setting of parenchymal lung disease.\(^13\)\(^-\)\(^14\)\(^,\)\(^17\)

In PH-ILD patients with concomitant RVF, the initial goal of therapy should focus on stabilization and improvement of RV function by rapidly decreasing the pulmonary vascular resistance (PVR), similar to the management of RVF in PAH.\(^18\) Once the RV function has improved sufficiently, it might be possible to manage patients long-term on inhaled prostacyclin therapy similar to patients in the INCREASE trial.\(^10\)\(^-\)\(^11\) Here, we report use of intravenous prostacyclin therapy in three PH-ILD patients to achieve stabilization and improvement in RV function followed by transition to maintenance inhaled prostacyclin therapy.

2. Methods
We performed a retrospective analysis of 3 consecutive PH-ILD patients admitted to a single tertiary academic center who presented with concomitant acute RVF. The diagnosis of ILD was confirmed by diffuse parenchymal lung disease on CT chest. The diagnosis of pre-capillary PH was confirmed by right heart catheterization (RHC) with mPAP ≥ 20 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and PVR > 3 Wood units (WU). Other causes of pre-capillary PH including chronic thromboembolic pulmonary hypertension (CTEPH) and connective tissue disease were excluded.

Acute RVF was defined by echocardiogram (TTE) and invasive hemodynamic data; criteria included RV dysfunction on echocardiogram (tricuspid annular planer systolic excursion (TAPSE) < 1.6 cm) as well as an elevated right atrial pressure (RAP ≥ 15 mmHg) and a depressed indirect Fick cardiac index (CI; < 2 L/min/m²).\textsuperscript{19-23}

2.1 Induction Protocol

During the index admission, all patients were newly diagnosed with PH-ILD and treatment naïve in regards to pulmonary vasodilator therapy. RHC was performed and an indwelling pulmonary artery catheter (PAC) secured in place for continuous hemodynamic monitoring in the intensive care unit (ICU). Patients received therapy for RVF intended for optimization of RV preload and contractility including continuous infusion of high-dose loop diuretics as well as vasopressors and/or inotropic agents.

In addition, RVF was treated with advanced prostacyclin therapy administered via peripherally inserted central catheter (PICC) line. Uptitration of advanced prostacyclin and subsequent optimization of RV afterload, in conjunction with RV preload and contractility, was guided by hemodynamics from the PAC. Goals of therapy were not only to achieve a target Fick CI of > 2 L/min/m² and PVR < 7 WU, but also to demonstrate echocardiographic changes in the RV as measured by TAPSE improvement by > 1 mm or TAPSE > 1.6 cm.\textsuperscript{10,19,24-27} CI, was calculated by the Fick principle where blood sampling was obtained from a systemic artery and the pulmonary artery to calculate the arterial-venous oxygen difference. Patients underwent daily TAPSE assessment by a critical care TTE board certified physician. The induction phase of advanced prostacyclin administration ended and the
transition to maintenance inhaled prostacyclin phase initiated when all transition criteria were fulfilled (Figure 1).

2.2 Transition Criteria

As the patient’s RV preload, contractility, and afterload were addressed by diuretics, vasopressors, inotropes, and advanced prostacyclin therapy during the induction phase, daily monitoring with PAC and TTE was performed to assess for candidacy of patient to enter the transition phase of the management protocol.

Transition criteria included PAC-derived hemodynamic improvement in CI to > 2 L/min/m$^2$. In conjunction with CI, a PVR < 7 WU was included in the transition criteria; this cut-off was chosen because the patients in the INCREASE trial had a mean PVR of 6.4 WU. Lastly, echocardiographic improvement in TAPSE by > 1 mm or TAPSE > 1.6 cm was also included.

When all 3 criteria (CI, PVR, and TAPSE) were fulfilled, patients were considered eligible for transition from the induction portion of the management protocol to the maintenance phase: transition from intravenous prostacyclin to inhaled prostacyclin (Figure 1).

2.3 Intravenous to Inhaled Prostacyclin Transition

Once criteria of CI, PVR, and TAPSE were fulfilled, patients were transitioned from intravenous prostacyclin to inhaled prostacyclin based on prior protocols. A conversion value of approximately 1 ng/kg/m$^2$ of intravenous treprostinil to 1 breath of inhaled treprostinil was utilized. The transition took place in the ICU over 24 hours. None of the patients suffered any major adverse events or side effects during this transition.

Figure 1: Induction Phase, Transition Criteria, and Maintenance Phase
3. Results

3.1 Baseline Clinical Characteristics

The baseline clinical characteristics of three PH-ILD patients are detailed in Table 1. The mean age was 75 years; two of the three patients were male (66.7%). Two patients had combined pulmonary fibrosis with emphysema (CPFE) and one patient had idiopathic pulmonary fibrosis (IPF); none of the patients had received antifibrotic therapy. All three patients required chronic supplemental oxygen therapy at the time of admission. None of the patients had been evaluated for PH as an outpatient prior to admission. Mean pro-BNP at time of admission was 15,753 pg/mL and all three patients exhibited signs of right heart failure on physical exam (Table 2).

3.2 Baseline RHC and TTE prior to PH Therapy

The invasive hemodynamics at time of initial, treatment-naive RHC are detailed in Table 3. The mean mPAP was 57 mmHg, mean PVR was 14.3 WU, and mean Fick CI was 1.8 L/min/m². Pre-treatment mean TAPSE obtained during index hospitalization TTE was 1.4 cm.

3.3 Index Hospitalization Characteristics

The patients had an average ICU length of stay (LOS) of 24.7 days (Table 4). All three patients initially required hemodynamic support with either an inotrope or vasopressor. Intravenous prostacyclin was initiated within four days of admission. The average dose of intravenous prostacyclin required to fulfill criteria for transition to maintenance therapy was 20.7 ng/kg/m² treprostinil (Table 5). Post-induction data including PVR, Fick CI, and TAPSE are presented in Table 5.
3.4 Longitudinal Outcomes in response to Maintenance Therapy

Three months after index hospitalization, patients underwent surveillance TTE and RHC (Table 6); mean PVR was 6.3 WU, mean Fick CI 2.2 L/min/m², and mean TAPSE 1.7 cm. Patients were not receiving any other pulmonary vasodilator therapy at the 3-month assessment except inhaled prostacyclin. None of the patients were re-admitted during this follow-up period and WHO FC improved from a mean of 4 prior to induction therapy to 3 at follow-up assessment.

4. Discussion

WHO Group 1 PAH patients with evidence of RV dysfunction resulting in depressed CI, elevated RAP and significantly elevated PVR are usually categorized as high-risk when assessed by various PAH risk calculators. In such patients, advanced prostacyclin therapy is indicated. A similar concept might be extrapolated to other forms of pre-capillary PH with concomitant RVF, including PH-ILD. However, long-term advanced prostacyclin therapy in PH-ILD is not standard of practice and VQ mismatch in the setting of parenchymal lung disease may occur. As such, administration of advanced prostacyclin therapy in PH-ILD patients with concomitant RV failure should only be performed in a closely monitored setting by an experienced PH specialist. None of the patients in this cohort had increasing supplemental oxygen requirements (Table 5). Additionally, the two CPFE patients had a favorable response to prostacyclin therapy despite observations from the INCREASE trial that would suggest otherwise.

Our case series of 3 PH-ILD patients with RVF lays the groundwork for a potential treatment algorithm for these complex patients, including utilization of intravenous prostacyclin during an induction phase with RHC and TTE-defined transition criteria leading to long-term maintenance therapy with inhaled prostacyclin.

4.1 Mirroring the Approach with Intravenous to Oral Treprostinil

The preliminary data from the recent EXPEDITE study of PAH patients created a protocol for transition from advanced prostacyclin therapy to a less invasive route of maintenance administration after an induction period. While the primary goal of the EXPEDITE study was to allow patients a chance to acclimate to the side effect profile of oral treprostinil by administering the drug intravenously
during the initial period, similar principles could potentially apply to the PH-ILD patient who has developed RVF. These patients may benefit from initial initiation of advanced prostacyclin to stabilize and improve RV function. Once this is achieved, patients could transition to inhaled prostacyclin therapy, which is not only an approved therapeutic option in this sub-population of pre-capillary PH, but is also less invasive, more patient-friendly, and has decreased likelihood of causing adverse events such as VQ mismatch.\textsuperscript{10-11,14,19}

4.2 What about Chronic RV disease?  
This approach of managing severe PH associated with acute RVF with an induction phase followed by maintenance therapy is novel; while it has its merits, such an approach may not apply to patients who have had long-standing RV dysfunction. These individuals may no longer have an adaptable RV that is capable of stabilizing and improving even with advanced prostacyclin therapy.\textsuperscript{34} To wit, the three patients in this report all presented with undiagnosed PH and acute RVF.

4.3 Choosing the Transition Criteria Metrics  
The justification for the RHC and TTE-derived transition criteria of CI, PVR, and TAPSE was based on prior evidence of each metric playing a significant role in the risk stratification of WHO Group 1 PAH patients as well as data obtained from the INCREASE trial.\textsuperscript{10,19,30-31} However, as this treatment algorithm is incorporated in the management of PH-ILD patients with RVF, we will be able to further refine the transition criteria metrics. As a result, the transition criteria will be tailored and adjusted with more experience and long-term follow-up in such patients; cut-offs may change, additional metrics added, and/or current parameters removed.

4.4 Effect on Resource Utilization – Length of Stay and Readmissions  
Another obvious issue with this approach to therapy, an induction phase with advanced prostacyclin therapy followed by transition to inhaled prostacyclin, in a closely monitored environment is the prolonged hospitalization required. In our case series, the ICU LOS alone was over 24 days. All three patients were suffering from significant deconditioning and required extensive rehabilitation while working towards a safe discharge. Nevertheless, while the ICU LOS may be significant during this
induction phase, the long-term benefit of stabilizing and improving RF function could, in contrast, prevent such patients from recurrent admissions for RVF, volume overload, and acute on chronic hypoxic respiratory failure. In this case series, none of the patients had re-admission to the hospital within the 3 months after discharge.

4.5 Limitations and Strengths

There are several limitations to this study: 1) it is a small case series of 3 patients without substantial longitudinal data beyond a 3-month period and 2) confounding factors such as inotrope and vasopressor assisted diuresis and its beneficial effects on invasive hemodynamics and subsequent improvement in PVR are unknown. The primary strength of the study is that it introduces a novel treatment algorithm into the management of PH-ILD patients who present with a severe RVF phenotype.

5. Conclusion

In this case series of three PH-ILD patients with RVF, we performed an induction phase of therapy with intravenous prostacyclin using echocardiographic and invasive hemodynamic monitoring followed by transition to maintenance therapy with inhaled prostacyclin prior to discharge. Further development of this treatment algorithm, potential testing in a clinical trial, and longer follow-up is warranted to improve the outcomes of patients with advanced PH-ILD and concomitant RVF.

Tables and Figures

Table 1: Clinical characteristics of PH-ILD patients with RVF at time of admission

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Age</th>
<th>Ethnicity</th>
<th>Sex</th>
<th>Prior Smoke</th>
<th>ILD type</th>
<th>Length of ILD dx (months)</th>
<th>Antifibrotic tx</th>
<th>FVC (%)</th>
<th>DLC O (%)</th>
<th>Use of supplemental oxygen</th>
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<td>M</td>
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Table 2: RVF signs and symptoms at time of admission

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<tr>
<th>Patient ID</th>
<th>JVD present</th>
<th>LE edema present</th>
<th>ProBNP (pg/mL)*</th>
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<td>8647</td>
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<td>Y</td>
<td>31501</td>
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<td>3</td>
<td>Y</td>
<td>Y</td>
<td>7111</td>
<td>4</td>
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</table>

*Normal range ProBNP: < 125 pg/mL

Table 3: RHC and TTE data prior to therapy initiation

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<tr>
<th>Patient ID</th>
<th>RA (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>PAWP (mmHg)</th>
<th>PVR (WU)</th>
<th>Fick CI</th>
<th>TAPSE (cm)</th>
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Table 4: Index hospitalization

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<tr>
<th>Patient ID</th>
<th>ICU LOS</th>
<th>Vasopressors [max dose]</th>
<th>Inotrope [max dose]</th>
<th>Continuous-infusion Diuretic [max dose]</th>
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<td>Norepinephrine [8 mcg/min] Vasopressin [0.03 u/min]</td>
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<td>Furosemide [25 mL/hr]</td>
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Table 5: RHC and TTE Measurements at time of Transition from IV to Inhaled Prostacyclin

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>IV Prostacyclin dose (ng/kg/m)</th>
<th>Supplemental O₂ needs compared to baseline</th>
<th>RAP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>PAWP (mmHg)</th>
<th>PVR (WU)</th>
<th>Fick CI</th>
<th>TAPSE (cm)</th>
<th>Inhaled Prostacyclin dose at discharge (breaths qid)</th>
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</table>


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<tr>
<th>Patient ID</th>
<th>Inhaled Prostacyclin dose (breaths qid)</th>
<th>RAP (mmHg)</th>
<th>mPAP (mmHg)</th>
<th>PAWP (mmHg)</th>
<th>PVR (WU)</th>
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<td>2.2</td>
<td>1.7</td>
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Table 6: Status 3 months after Discharge

*Patient 1 was discharged on a dose of 24 breaths qid but titrated down to 18 breaths qid due to side effects of headache and cough.
References


