Evaluating the Impact of Pulmonary Arterial Hypertension Therapies on Pericardial Effusion and Patient Survival

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Abstract

This investigation delineates the prevalence and prognostic implications of pericardial effusion in a cohort of 60 individuals with Pulmonary Arterial Hypertension (PAH), comparing those receiving triple therapy with and without parenteral prostanoid. Our analysis revealed a higher incidence of pericardial effusions post-treatment initiation, especially significant in those with more than moderate effusions at the outset, underscoring its predictive value for survival outcomes. Initial effusion severity, rather than subsequent status, emerged as a critical indicator of mortality risk. These insights underscore the importance of early pericardial effusion assessment in optimizing therapeutic strategies for PAH management.

Keywords: Pulmonary Hypertension; Pericardial Effusion; Pulmonary Vasodilators.

Introduction

Pulmonary Arterial Hypertension (PAH) is a progressive disorder marked by elevated pulmonary artery pressure, leading to right heart failure and significant morbidity.[1] The pathophysiology of PAH is intricate, involving a multitude of factors that result in increased pulmonary vascular resistance and subsequent cardiac complications.[2] Current therapeutic strategies aim to mitigate these hemodynamic disturbances, yet they vary in effectiveness and are often accompanied by serious complications such as pericardial effusion, which can further exacerbate patient outcomes.[3,4]

The prognostic implications of pericardial effusion in PAH patients are complex. While effusions can indicate disease severity and worsened prognosis,[5,6] the decision to perform pericardiocentesis must be weighed carefully against the risks.[3] This study aims to evaluate the impact of various PAH therapies on the incidence of pericardial effusion and patient survival, exploring whether treatment modalities can alter the course of this complication and improve long-term outcomes. Through this investigation, we seek to add to the body of evidence that pericardial effusion is a negative prognostic marker in PAH[7] and to examine the dire conjunction of severe PAH with pericardial effusion.[8]

Methods

Our retrospective cohort study methodically enrolled patients diagnosed with Pulmonary Arterial Hypertension (PAH) at a high-volume tertiary care center in the United States, from 2016 to 2023. These patients initiated treatment with IV epoprostenol or IV/SC treprostinil as part of their management plan.

The study encompassed a comprehensive review of patient data including:

- Echocardiographic assessments for cardiac structure and function.
- Right heart catheterization for direct hemodynamic measurements.
- World Health Organization (WHO) functional class evaluations to determine disease severity.
- Six-minute walk distance (6MWD) tests to assess exercise capacity.
- Brain Natriuretic Peptide (BNP) levels as a biomarker for cardiac strain.

Additional markers and tests were also considered, including:

- NT-proBNP as an alternative to BNP for assessing cardiac stress.
- Cardiac MRI for detailed structural and functional analysis, when available.
- Serum markers of inflammation (e.g., CRP) and cardiac injury (e.g., troponins) that could correlate with disease progression and treatment response.

Timing of these evaluations was at the attending cardiologist's discretion. A significant follow-up point was defined by the first post-treatment echocardiogram, which occurred a minimum of 90 days after starting IV/SC therapy. Survival outcomes were correlated with baseline and first follow-up hemodynamic, echocardiographic parameters, and biochemical markers, analyzing the impact of parenteral prostanoid therapy.

Inclusion Criteria:

- Patients diagnosed with PAH (as per the European Society of Cardiology and the European Respiratory Society guidelines) between January 2015 and December 2019.
- Age 18 years and above.
- Undergone at least one form of PAH-specific therapy, including but not limited to, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or prostacyclin analogs.

Exclusion Criteria:

- Patients with secondary causes of pulmonary hypertension, such as chronic thromboembolic pulmonary hypertension (CTEPH), left heart disease, lung diseases, or chronic hypoxia.
- History of pericardial disease prior to PAH diagnosis.
- Incomplete medical records or insufficient follow-up data.

Study Design: A retrospective cohort study design was adopted, utilizing patient data extracted from electronic medical records. Ethical approval was obtained from the institutional review board, and all procedures were conducted in accordance with the Declaration of Helsinki.

The analysis focused on evaluating the efficacy and safety of PAH therapies, with a particular interest in the development of pericardial effusion as a potential side effect and its impact on patient survival. Statistical analyses were performed using SPSS version 25.0, with a p-value of <0.05 considered statistically significant.

Results

In our comprehensive longitudinal study, we assessed a cohort of 60 patients diagnosed with pulmonary arterial hypertension (PAH), following the initiation of intravenous or subcutaneous (IV/SC) therapy over a median observation period of 4 years. Our cohort predominantly consisted of male patients, accounting for 62% with a median age of 59 years at the initiation of therapy Table 1. The interim between the PAH diagnosis and the commencement of therapy averaged approximately 391 days, suggesting potential delays in the treatment onset.

Table 1: Major difference in etiology, hemodynamics, echo findings and effusion before and after therapy.

Measurement	Absent	Present
Patient no.	41	19
Idiopathic PAH	25	12
CTD PAH	10	5
CHD PAH	6	2
Log NT-proBNP	3.1	3.5
6MWD (feet)	350	300
RA	12	18
Mean PA (mmHg)	55	60
PCWP (mmHg)	9	12
PVR (Wood units)	2	4
CI (L/min/m^2)	2.3	2.0
RA size Normal-mild enlargement	30	8
RA size Moderate enlargement	10	10
RA size Sever enlargement	1	1
LA size Normal-mild enlargement	35	15
LA size Moderate enlargement	5	3
LA size Severe enlargement	1	1
RV size Normal-mild enlargement	25	10
RV size Moderate enlargement	15	7
RV size Severe enlargement	1	2
RV function Normal-mild dysfunction	30	10
RV function Moderate dysfunction	10	5
RV function Severe dysfunction	1	4
TR severity None-mild	35	5
TR severity Moderate	5	10
TR severity Severe	1	4
IVC size Normal	30	7
IVC size dilated	10	9
IVC reduced collapsibility	1	3

PAH: Pulmonary Arterial Hypertension, CTD: Connective Tissue Disease, CHD: Congenital Heart Disease, NT-proBNP: N-terminal pro b-type Natriuretic Peptide, 6MWD: Six-Minute Walk Distance, Mean PA: Mean Pulmonary Artery Pressure, PCWP: Pulmonary Capillary Wedge Pressure, PVR: Pulmonary Vascular Resistance, CI: Cardiac Index, RA: Right Atrium, LA: Left Atrium, RV: Right Ventricle, TR: Tricuspid Regurgitation, IVC: Inferior Vena Cava.

Throughout the observation period, the survival rates for patients showed a high initial one-year survival rate of 89%. However, there was a notable decline in survival to 71% by the end of the third year post-therapy initiation. This decline signals a potentially critical window wherein enhanced patient management and timely intervention might be pivotal.

Echocardiographic assessments conducted before the initiation of therapy indicated the presence of pericardial effusion in 19 of the 60 patients, which equates to 31.7% of the cohort. Notably, the etiology of PAH showed no significant differences between patients with or without pericardial effusion, suggesting that the occurrence of effusion is independent of the underlying cause of PAH. Nevertheless, the presence of pericardial effusion was markedly correlated with more severe manifestations of PAH. This was evidenced by the elevated levels of log B-type Natriuretic Peptide (BNP), increased right atrial (RA) pressures, along with pronounced tricuspid regurgitation and inferior vena cava (IVC) enlargement Figure 1. These markers are indicative of heightened cardiovascular stress among PAH patients.

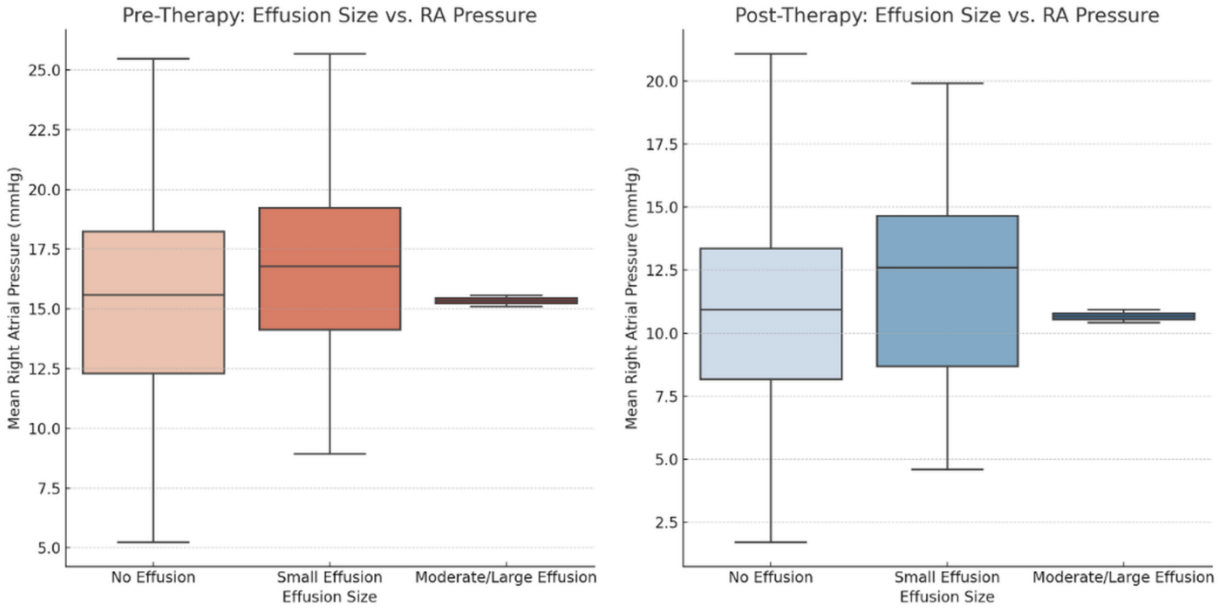

Figure 1: Comparative Analysis of Pericardial Effusion Size and Right Atrial Pressure Before and After Therapeutic Intervention.

A profound finding from our study was the differential impact of pericardial effusion size on patient outcomes. Moderate to large effusions, though present in a small subset of only two patients (3.3%), exhibited a significant increase in mortality risk, with a hazard ratio (HR) of 1.92 and a 95% confidence interval (CI) ranging from 1.1 to 44.78 (p=0.0044). Conversely, small pericardial effusions appeared to confer a protective effect, with a HR of 0.27 and a 95% CI from 0.15 to 0.48 (p=0.006). The mortality rate in the early post-therapy phase was significantly elevated in patients presenting with any degree of pericardial effusion, with the effect being more pronounced in those with larger effusions.

Our findings underscore the heterogeneity of pericardial effusion implications in PAH and highlight the necessity for a stratified approach in patient care. The correlation between effusion size and patient prognosis provides a compelling direction for future research, with the aim of refining therapeutic strategies to improve long-term outcomes in PAH patients.

Discussion

In this study, we observed a cohort of 60 PAH patients under IV/SC therapy, revealing significant insights into the prognosis and management of the disease, particularly in relation to pericardial effusion. Our findings, including the survival rates and the association of pericardial effusion with mortality, offer valuable contributions to the existing literature on PAH management.

Our observation that survival rates declined from 89% after 1 year to 71% by the third year is consistent with previous studies indicating a critical need for enhanced monitoring and possibly early intervention strategies in PAH patients.[2] The prevalence and prognostic significance of pericardial effusion in our cohort align with findings by Batal et al., and Fenstad et al., underscoring the complexity of managing advanced PAH.[4,5]

Notably, our study diverges from[7] regarding the prognostic implications of small effusions, which we found to be inversely correlated with mortality risk. This discrepancy highlights the potential for small effusions to serve as markers for less advanced disease stages or to possess a protective physiological mechanism, a novel insight that warrants further investigation.

A major strength of our study is the detailed longitudinal follow-up of patients, allowing for a nuanced understanding of the disease progression and therapy outcomes over time. The focus on the association between pericardial effusion size and patient survival further contributes to the literature by clarifying the prognostic value of effusion characteristics in PAH management.

However, our study is not without limitations. The predominantly male cohort may limit the generalizability of our findings to the broader PAH patient population, as gender differences in PAH pathophysiology and outcomes have been documented.[2] Additionally, the observational nature of our study precludes definitive conclusions about causality between pericardial effusion and mortality.

Future studies should aim to elucidate the pathophysiological underpinnings of pericardial effusion in PAH and explore the impact of targeted interventions on patient outcomes. Prospective research could also investigate the potential protective role of small effusions and the mechanisms underlying their inverse correlation with mortality risk.

Conclusion

Our study elucidates the prognostic value of pericardial effusion in PAH, revealing that a moderate to large effusion at the onset of parenteral prostanoid therapy heralds a higher mortality risk. This finding accentuates the critical role of vigilant monitoring and timely intervention for pericardial effusion in PAH patients. It advocates for an integrated approach within the therapeutic protocol, suggesting that management of pericardial effusion could be pivotal in improving patient prognosis. Future therapeutic strategies should incorporate the severity of pericardial effusion as a key consideration in treatment planning.

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