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Review

Sildenafil for Worsening Group 3 Pulmonary Hypertension in CPFE: A Case of Rapid Recovery from Acute Hypoxic Respiratory Failure: Is RV-PA Uncoupling the Key

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ABSTRACT

We report the case of an 81-year-old male with combined pulmonary fibrosis and emphysema (CPFE), idiopathic pulmonary fibrosis (IPF) and WHO Group 3 pulmonary hypertension (PH), who presented with acute on chronic hypoxic respiratory failure. Imaging revealed sub-segmental pulmonary embolism (PE) and right heart catheterization confirmed worsening PH with poor right ventricular-pulmonary artery (RV-PA) coupling. Despite the severity of his condition, the patient demonstrated rapid and sustained improvement in oxygenation following the initiation and titration of sildenafil. This case highlights the diagnostic and therapeutic challenges in managing CPFE with superimposed PE and underscores the potential role of pulmonary vasodilator therapy in select patients with advanced Group 3 PH.

Keywords: Combined pulmonary fibrosis and emphysema, pulmonary hypertension, sildenafil, pulmonary embolism, RV-PA coupling, case report

Introduction

Combined pulmonary fibrosis and emphysema (CPFE) is a distinct clinical entity characterized by upper-lobe emphysema and lower-lobe fibrosis, often associated with severe pulmonary hypertension (PH) and poor gas exchange. PH in CPFE is typically classified as WHO Group 3 and is associated with increased morbidity and mortality[1]. Acute decompensation in CPFE may result from infection, thromboembolic events or disease progression. The role of pulmonary vasodilators in Group 3 PH remains controversial due to concerns about ventilation-perfusion mismatch, but emerging evidence suggests potential benefit in select patients with right ventricular (RV) dysfunction and poor RV-PA coupling[2-4].

Case Presentation

An 81-year-old male with chronic hypoxic respiratory failure secondary to CPFE, IPF and WHO Group 3 PH presented to the emergency department with worsening dyspnea and non-massive hemoptysis. His baseline oxygen requirement was 8-10 L/min. On arrival, he was hypoxic with saturations in the 70s despite 10 L/min of oxygen. He was immediately placed on heated high flow oxygen at 60% FiO2 and 40 l/min. He denied any recent travel, sick contacts.

His medical history included dyslipidemia, benign prostatic

hyperplasia, depression, hypothyroidism, transient ischemic attack, non-obstructive coronary artery disease, peripheral vascular disease, glaucoma and meralgia paresthetica. He had a 60–80 pack-year smoking history, quit in 2021 Patient reported long standing significant exposure to automobile fumes. He has been following with pulmonology clinic for the last 6 months. His ambulatory medications include Nintedanib 150 mg BID for pulmonary fibrosis, Inhaled Treprostinil 64mcg QID for his pulmonary hypertension. It could not be titrated up due to adverse effects.

On examination, he was in mild to moderate respiratory distress, requiring heated high-flow oxygen at 40 L/min and 60% FiO_2. He was hemodynamically stable with blood pressure of 114/70, respiratory rate of 26/min and afebrile. Physical exam revealed bilateral crepitations, a systolic murmur and digital clubbing. Neurologically, he was alert and oriented.

CT pulmonary angiography revealed acute sub-segmental PE in the right lower lobe and possible embolism in the left lower lobe. Background findings included a UIP-pattern of fibrosis, upper-lobe emphysema, bilateral traction bronchiectasis and mildly enlarged mediastinal and hilar lymphadenopathy **(Figures 1-4)**.

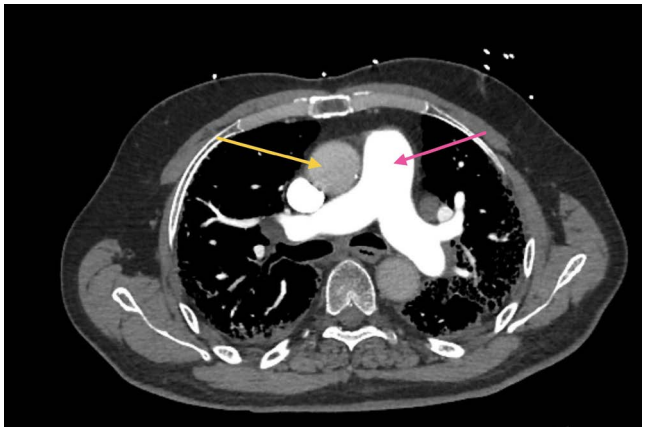

Figure 1: CT Chest with IV contrast, axial view, soft tissue window, at the level of pulmonary artery demonstrating enlarged pulmonary artery compared to aorta, which is highly suggestive of pulmonary arterial hypertension

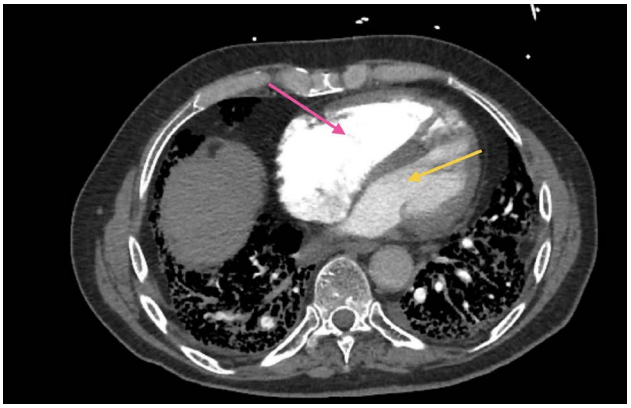

Figure 2: CT Chest with IV contrast, axial view, soft tissue window, at the level of ventricles demonstrating enlarged right ventricle (pink arrow) compared to left ventricle (yellow arrow), which is highly suggestive of pulmonary arterial hypertension or right ventricular overload

Patient was started on heparin infusion, empiric antibiotics and corticosteroids and admitted to a medical progressive unit. Antibiotics and steroids were discontinued after negative infectious workup (negative procalcitonin, negative CRP) and stable radiographic findings when compared to his old Computer tomography scans. His ambulatory medications were continued which included Nintedanib, Inhaled Treprostinil and other inhaled therapies-Budesonide, Arformoterol and Revefenacin. Heparin was later transitioned to Apixaban after hemoptysis subsided.

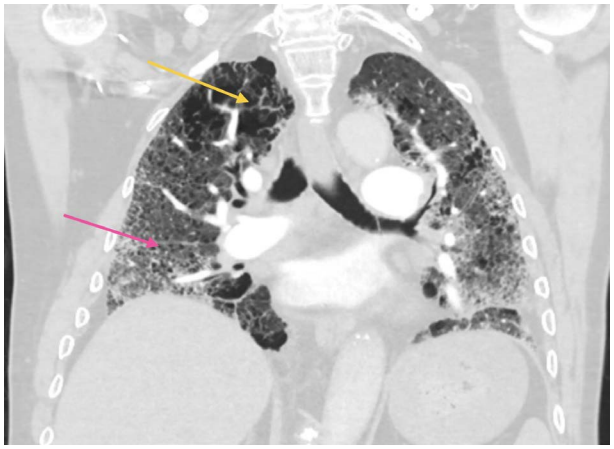

Figure 3: CT Chest with IV contrast, coronal view, lung window, demonstrating severe emphysema in the upper lobes (yellow arrow) and honey combing in the lower lobe's indicative of fibrosis (pink arrow). This pattern is consistent with Combined Pulmonary fibrosis with emphysema.

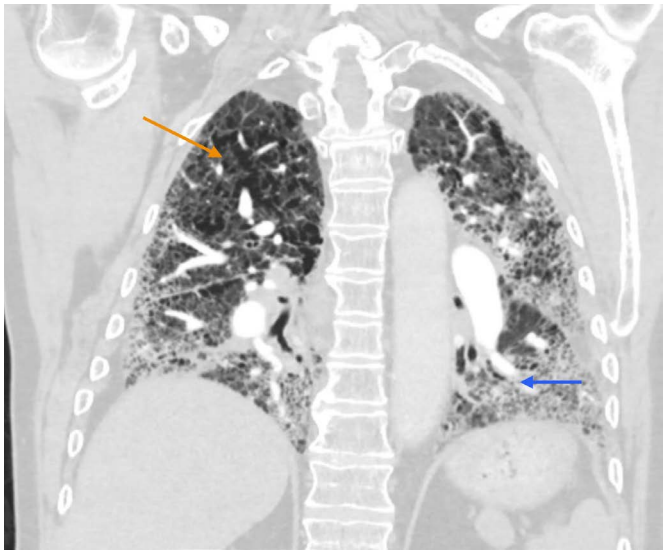

Figure 4: CT Chest with IV contrast, coronal view, lung window, demonstrating severe emphysema in the upper lobes (orange arrow) and severe honey combing in the lower lobe's indicative of fibrosis (blue arrow). This pattern is consistent with Combined Pulmonary fibrosis with emphysema.

His Pulmonary function tests obtained 3 months prior showed preserved FVC (110%) and FEV_2 (113%) with reduced TLC (75%) and severely decreased DLCO (20%). A six-minute walk test revealed a distance of 259 meters with a nadir SpO_2 of 91% on 10 L/min oxygen.

Echocardiography on the day of admission revealed normal left ventricular function (LVEF 55–60%), RV enlargement with mildly reduced systolic function and estimated pulmonary artery systolic pressure of 75 mm Hg with diastolic septal flattening suggestive of increased right ventricular filling pressures,

enlarged right atrium and moderate tricuspid regurgitation. The TAPSE/SPAP ratio was 0.272 **(Figures 5-9)**.

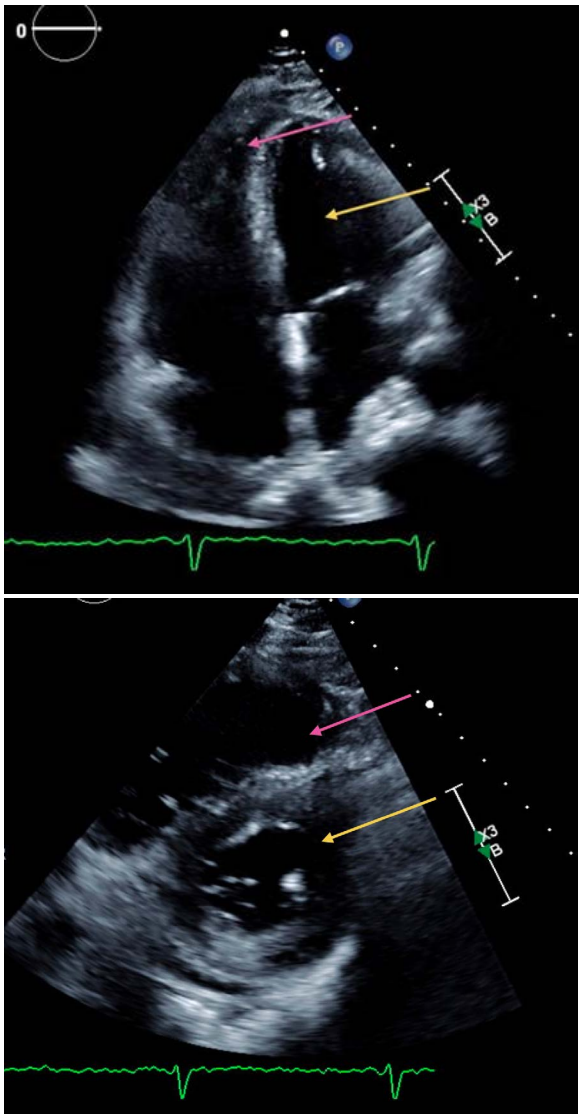

Figure 5: 2D Echocardiogram, Apical 4 chamber view demonstrating enlarged right ventricle (pink arrow) compared to left ventricle (yellow arrow). As can be seen here, the majority of the apex in this view is dominated by right ventricle suggesting right ventricular overload.

Figure 6: 2D Echocardiogram, Parasternal short axis view demonstrating enlarged right ventricle (pink arrow) compared to left ventricle (yellow arrow) confirming right ventricular overload.

Right heart catheterization confirmed severe PH with mean PAP (Pulmonary artery pressure) of 31 mmHg, PVR (pulmonary vascular resistance) of 10 WU, Right ventricle DP/DT of 528 and Fick cardiac index of 1.49 L/min/m². Left ventricular stroke work index was noted to be 36.71. The right heart catherization findings were significantly worse than the one that was obtained 3 months ago which revealed a PVR of 3.5 WU and cardiac index of 2.5 L/min/m2. His prior coronary angiogram obtained 3 months ago revealed 30-40% stenosis of left main coronary arteries, otherwise only mild irregularities were noted in the rest of the coronary arteries.

Due to persistent hypoxia despite anticoagulation for 72 hours needing heated high flow at 60% FiO2 and 40 l/min, sildenafil 20 mg TID was initiated, as a therapeutic trial after a shared decision process involving risks versus benefit. Within six hours of sildenafil initiation, FiO_2 requirements decreased from 60% to 40%. The dose was further increased after 48 hours to 40 mg TID without adverse effects. Oxygen needs returned to baseline within 24 hours needing 8- 10 l/min in the next 36 hours.

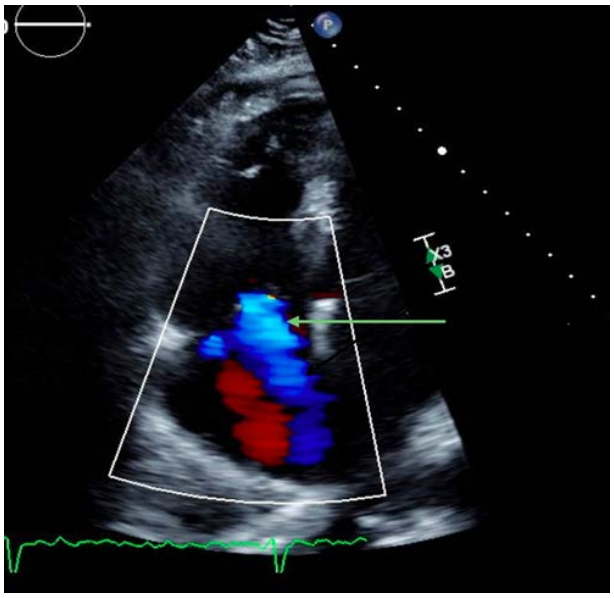

Figure 7: 2D Echocardiogram, Color doppler demonstrating tricuspid regurgitation (green arrow), an indirect marker of severity of pulmonary hypertension.

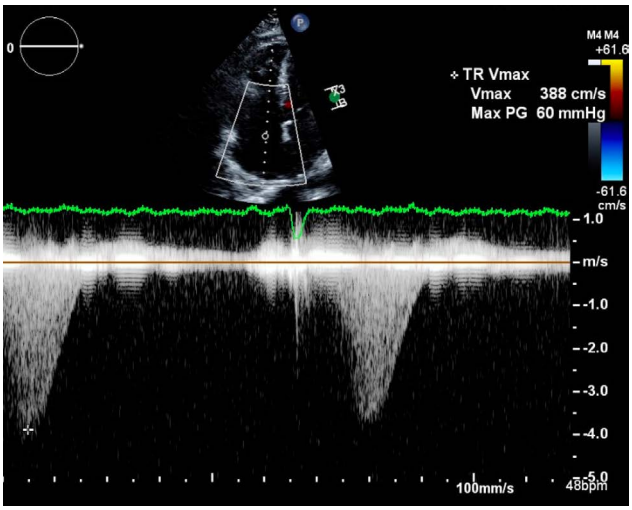

Figure 8: 2D Echocardiogram, Continuous wave doppler estimated tricuspid velocity of 3.88m/sec highly suggestive of pulmonary hypertension.

The patient declined referral to a pulmonary hypertension center due to travel concerns. He was discharged on sildenafil 40 mg TID and inhaled Treprostinil. At three-month follow-up, he remained stable on baseline oxygen and medications. A perfusion scan showed low probability of pulmonary embolism.

Discussion

Combined pulmonary fibrosis and emphysema (CPFE) is a complex and under recognized syndrome characterized by the coexistence of upper-lobe emphysema and lower-lobe fibrosis, typically in older male smokers. It is associated with relatively preserved spirometry but severely reduced diffusing capacity (DLCO), profound hypoxemia and a high prevalence of pulmonary hypertension (PH), particularly WHO

Group 3 PH due to chronic lung disease and hypoxia[1,2]. The pathophysiology of PH in CPFE is multifactorial, involving hypoxic vasoconstriction, vascular remodeling and destruction of the pulmonary capillary bed[3]. The presence of PH in CPFE is associated with significantly worse outcomes, including reduced exercise capacity and survival[4]. The management of CPFE remains largely supportive, with no disease-specific therapies. Treatment strategies include supplemental oxygen, pulmonary rehabilitation and management of comorbidities. Lung transplantation is considered in advanced cases, although many patients are ineligible due to age or comorbidities[3,4].

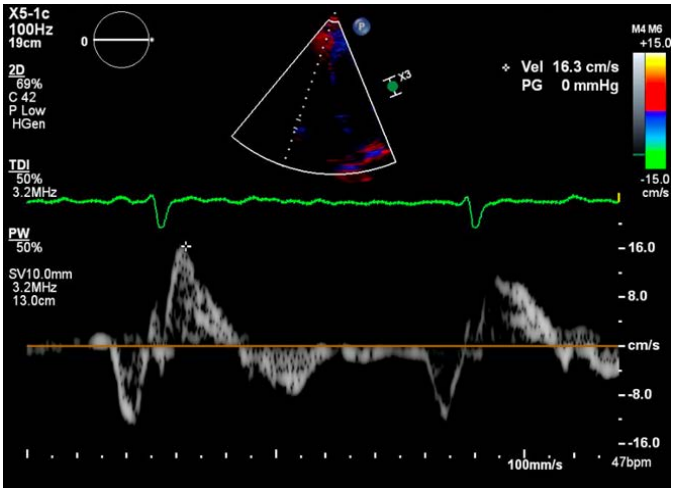

Figure 9: 2D Echocardiogram, Tissue doppler imaging of the right ventricle.

While the use of pulmonary vasodilators in WHO Group 3 PH is not routinely recommended due to concerns about worsening ventilation-perfusion mismatch, emerging evidence suggests that a subset of patients with severe PH and right ventricular (RV) dysfunction may benefit from targeted therapy[4,5].

Our patient had severe combined pulmonary fibrosis and emphysema with relatively preserved spirometry and decreased DLCO. He had evidence of pulmonary hypertension and tolerated Inhaled Treprostinil that was initiated in the outpatient setting.

Our patient's acute decompensation was precipitated by a sub-segmental PE. Although often considered clinically insignificant, sub-segmental emboli can be hemodynamically destabilizing in patients with pre-existing PH and limited cardiopulmonary reserve. The PE likely exacerbated RV dysfunction, contributing to worsening hypoxia and increased oxygen requirements.

The evidence regarding the use of systemic pulmonary vasodilators in Group III pulmonary hypertension is not clear with conflicting findings. The guidelines recommend initiating inhaled Treprostinil for Group III pulmonary hypertension associated with pulmonary fibrosis, but not emphysema.

Inhaled Treprostinil, a prostacyclin analog, has recently emerged as a promising therapy for Group 3 PH. The INCREASE trial demonstrated that inhaled Treprostinil significantly improved 6-minute walk distance, reduced NT-proBNP levels and delayed clinical worsening in patients with PH due to ILD, including CPFE[6]. Unlike systemic vasodilators, inhaled agents offer the advantage of targeted pulmonary vasodilation with minimal systemic effects, potentially reducing the risk of ventilation-perfusion mismatch. Our patient was already on inhaled Treprostinil at baseline and continued therapy during hospitalization and follow-up, likely contributing to his clinical stability.

In patients with Group III pulmonary hypertension, it is generally recommended to avoid endothelial antagonists, however phosphodiesterase inhibitors may be considered in select patients, however it is still unclear who would benefit the most[3,4]. It is likely that RV-PA (Right Ventricle-Pulmonary artery) uncoupling may play a role to determine a response to systemic pulmonary vasodilator therapy in patients with CPFE associated with severe pulmonary hypertension.

RV-PA coupling describes the relationship between RV contractility and pulmonary arterial afterload. It is a critical determinant of RV efficiency and adaptation in PH. The gold standard for assessing RV-PA coupling is the ratio of end-systolic elastance (Ees) to arterial elastance (Ea), but surrogate markers such as TAPSE/SPAP and stroke volume/end-systolic volume ratios are increasingly used in clinical practice. Studies have shown that impaired RV-PA coupling is associated with worse exercise capacity, clinical deterioration and mortality in PH patients[7,8].

Despite anti-coagulation, his oxygen requirements persisted beyond 72 hours. On the right heart catheterization, the presence of a markedly elevated pulmonary vascular resistance (10 WU), reduced cardiac index (1.49 L/min/m²) and a low TAPSE/SPAP ratio (0.272) indicated poor RV-pulmonary artery (RV-PA) coupling, which prompted us to consider Sildenafil therapy.

Sildenafil, a phosphodiesterase-5 inhibitor, is FDA-approved for WHO Group 1 pulmonary arterial hypertension (PAH) and has demonstrated benefits in improving exercise capacity, pulmonary hemodynamics and quality of life[5]. Although its use in Group 3 PH is off-label, small studies and case reports have shown that sildenafil may improve oxygenation and RV function in select patients with interstitial lung disease (ILD)-associated PH, particularly those with evidence of RV-PA uncoupling[9,10]. In our case, the patient has evidence of impaired RV-PA coupling and experienced a rapid and sustained improvement in oxygenation following sildenafil initiation, supporting its potential utility in this context. The temporal improvement strongly suggests the role of sildenafil. Although, other possibilities remain that either the complete effect of anticoagulation was delayed beyond 72 hours or the possibility of improvement in right ventricular function.

Interestingly, sildenafil has also been explored in the setting of acute pulmonary embolism (PE). Experimental models and case reports suggest that sildenafil may reduce pulmonary vascular resistance and improve RV function in acute PE by promoting pulmonary vasodilation[11,12]. A randomized trial in patients with intermediate-high risk PE found that a single dose of sildenafil did not significantly improve cardiac index but did lower systemic blood pressure, highlighting the need for further research[13]. In our patient, the combination of sub-segmental PE and pre-existing PH likely precipitated acute RV decompensation. The favorable response to sildenafil suggests that pulmonary vasodilation may have mitigated RV afterload and improved oxygenation, even in the acute setting, especially in the presence of impaired RV-PA coupling.

This case underscores the importance of individualized therapy in CPFE with severe PH. While guidelines caution against routine use of vasodilators in Group 3 PH, our patient's hemodynamic profile and clinical trajectory justified a trial of sildenafil, which resulted in marked improvement. The TAPSE/SPAP ratio, a noninvasive marker of RV-PA coupling, has been shown to predict outcomes in PH and guided our therapeutic decision. The combination of inhaled Treprostinil and sildenafil may offer synergistic benefits in select patients, although further studies are needed to define optimal treatment strategies.

Conclusion

This case illustrates the diagnostic and therapeutic complexity of managing CPFE with superimposed PE and severe pulmonary hypertension. While pulmonary vasodilators are not routinely recommended for WHO Group 3 PH, this case supports their use in select patients with evidence of RV-PA uncoupling and hemodynamic compromise. Further research is needed to identify which patients may benefit from such therapies.

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