Literature Review

Supraventricular Arrhythmias in Idiopathic Pulmonary Fibrosis: Clinical Links and Implications

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Abstract

Idiopathic pulmonary fibrosis (IPF) and supraventricular arrhythmias (SVAs) share a profound pathophysiological connection beyond incidental comorbidity. This review synthesizes current evidence demonstrating how progressive pulmonary fibrosis creates an arrhythmogenic cardiac substrate through three interdependent pathways. Pulmonary hypertension imposes chronic pressure overload on the right heart, leading to right atrial dilation, interstitial fibrosis, gap junction dysfunction, and electrical remodeling, creating conditions for re-entrant circuits. Chronic hypoxemia induces intracellular calcium overload, after-depolarizations, and sympathetic overactivity, providing functional arrhythmogenic triggers independent of structural remodeling. These mechanisms collectively transform the atrial myocardium into a vulnerable environment where re-entrant circuits and triggered activity persist. The resulting SVAs, particularly atrial fibrillation and flutter, are strongly associated with IPF's cardiopulmonary pathophysiology. This integrated perspective challenges clinicians to view IPF not as an isolated lung disease but as a systemic syndrome with significant cardiac implications. However, current evidence is largely observational, and further prospective studies are needed to establish screening and management guidelines.

Keywords: cardiopulmonary interaction, IPF, pulmonary hypertension, SVA

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is characterized by relentless scarring of the lung parenchyma. With the advent of antifibrotic therapies, IPF patients are living longer with advanced disease, facing growing cumulative exposure to arrhythmogenic substrates.

Central to this risk is pulmonary hypertension, which imposes chronic pressure overload on the right heart, leading to right atrial dilation, structural remodeling, and interstitial fibrosis, a pro-arrhythmic environment. Compounded by chronic hypoxemia and systemic inflammation, the stage is set for electrical instability and re-entrant circuits manifesting as supraventricular arrhythmias (SVAs).

Despite growing evidence linking IPF to SVAs, significant knowledge gaps remain. No randomized controlled trials have evaluated antiarrhythmic strategies in IPF, and no clinical guidelines address SVA screening or management in this population. This review synthesizes available evidence to guide future research and clinical practice.

IDIOPATHIC PULMONARY FIBROSIS AND SUPRAVENTRICULAR ARRHYTHMIA

Definition

Idiopathic pulmonary fibrosis is a progressive, fatal fibrotic interstitial lung disease of unknown etiology, characterized by a usual interstitial pneumonia (UIP) pattern on imaging or histopathology.[1–3] It predominantly affects the subpleural and basal lung regions, with relentless progression and poor prognosis.[1,2,4] The diagnosis requires multidisciplinary exclusion of other causes,

per 2022 international guidelines.[2] Although not part of formal diagnostic criteria, IPF frequently coexists with cardiovascular complications, particularly pulmonary hypertension and arrhythmias, which substantially impact morbidity and mortality.[2]

Supraventricular arrhythmias (SVAs) are abnormal cardiac rhythms originating from or sustained by structures above the ventricular myocardium, including the sinoatrial node, atria, atrioventricular node, and proximal His bundle. The characteristic electrocardiographic manifestation is a narrow QRS complex tachycardia (<120 ms), reflecting ventricular activation through the intact His-Purkinje system.[5]

Supraventricular arrhythmias encompass atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular nodal re-entrant tachycardia (AVNRT), and atrioventricular re-entrant tachycardia (AVRT). The fundamental mechanisms include abnormal impulse initiation (enhanced automaticity or triggered activity) and abnormal impulse conduction (re-entrant circuits), potentiated by structural alterations such as atrial fibrosis, chamber dilation, inflammation, and autonomic imbalance.[5,6]

Epidemiology

Idiopathic pulmonary fibrosis exhibits substantial epidemiological heterogeneity globally. This reflects variations in diagnostic criteria, case definitions, study methodologies, and population demographics.[1,7] It represents approximately 17–37% of all interstitial lung disease diagnoses. It demonstrates a strong demographic predilection for older adults, with marked male predominance, and rarely occurs before age 50.[1,7,8]

In addition to the growing burden of IPF itself, SVAs, particularly atrial fibrillation, are increasingly recognized as common comorbidities in this population. A 2025 meta-analysis by Li et al. encompassing 28 observational studies demonstrated that patients with IPF face a significantly elevated risk of arrhythmia, with an odds ratio of 1.34 compared to non-IPF controls. This finding underscores SVAs as a clinically relevant comorbidity in the IPF population.[6]

Global incidence estimates range from 1 to 13 cases per 100,000 persons annually, while prevalence ranges from 3 to 45 cases per 100,000.[1,7–9] Rising incidence and prevalence have been documented worldwide. In Europe, a Finnish study reported a nearly fivefold increase in IPF incidence over 17 years.[10] While in Asia, Japan and South Korea have also demonstrated significant increases in IPF prevalence, partially attributable to population aging, widespread adoption of high-resolution computed tomography (HRCT), and increased clinical awareness.[11–13]

Despite methodological challenges in data interpretation, longitudinal studies consistently demonstrate rising incidence and prevalence trends. For example, an analysis from the United States reported a doubling of IPF prevalence between 2000 and 2012.[1] This observed increase likely reflects evolving diagnostic criteria, enhanced utilization of high-resolution computed tomography, and improved disease recognition in clinical practice. However, as of 2025, no population-based epidemiological studies on IPF have been conducted in Indonesia.

Risk Factors

The development of IPF results from a complex interplay of genetic susceptibility, environmental exposures, demographic factors, and comorbidities.[1,14] Advanced age is the strongest demographic risk factor. The disease is exceedingly rare before age 50, with incidence rising exponentially thereafter.[1,15] Biologically, aging drives cellular senescence and telomere attrition in alveolar epithelial cells, creating a pro-fibrotic, pro-inflammatory milieu that promotes fibroblast activation and progressive fibrosis.[4,8,14,16]

Male sex confers a 1.5 to 2-fold increased risk of IPF. While historically attributed to higher smoking rates and occupational exposures, emerging evidence suggests intrinsic biological differences, including hormonal influences, sex-specific genetic susceptibilities, and variations in immune and wound-healing responses, may also contribute.[1,8,16] Genome-wide association studies have identified several risk loci with stronger effect sizes in males.[1,7,17]

Genetic predisposition is fundamental to IPF risk. Familial clustering occurs in approximately 20% of cases, though most genetic risk is polygenic.[1,8,14] The strongest genetic risk factor is a gain-of-function promoter variant in the mucin 5B gene (MUC5B rs35705950), present in 30–35% of sporadic IPF cases of European descent and over 50% of familial cases.[18–21] The variant likely promotes fibrosis by disrupting mucociliary clearance, impairing host defense, and altering the airway microenvironment.[18–20]

Mutations in telomere maintenance genes (TERT, TERC, RTEL1, and PARN) and surfactant genes (SFTPC and SFTPA2) are strongly associated with familial pulmonary fibrosis. Shortened leukocyte telomeres serve as a biomarker of disease risk and accelerated progression, even without identifiable mutations, linking biological aging to IPF pathogenesis.[1,8,14,22]

Cigarette smoking is the most significant modifiable environmental risk factor for IPF.[1,14] Current and former smokers have a 1.6 to 2.9-fold increased risk of developing IPF compared to never-smokers.[1,14,21] Smoking is believed to act through multiple mechanisms. These include inducing oxidative stress, causing direct epithelial injury, promoting apoptosis, and altering the lung microbiome. Crucially, smoking in IPF patients is also associated with a more rapid decline in lung function and poorer survival outcomes.[14,16,21].

Occupational and environmental exposures to various organic and inorganic dusts, fumes, and gases contribute significantly to disease risk. Key implicated agents include metal dusts (e.g., steel, lead, and brass), wood dusts, stone/silica dust, agricultural dusts, livestock farming exposures, automotive emissions, and other industrial pollutants.[1,23,24] Large-scale case-control and cohort studies have consistently linked these exposures to IPF. This suggests a role for chronic, low-grade inhalation injury in disease initiation. The risk appears to be dose-dependent and may interact synergistically with genetic susceptibility.[4,14,25]

Air pollution, particularly long-term exposure to ambient particulate matter (PM2.5 and PM10), nitrogen dioxide (NO_2), and ozone (O_3), has emerged as a significant environmental risk factor.[14,23,24] Proposed mechanisms include pollutant-induced oxidative stress, systemic inflammation, and direct epithelial damage. Epidemiological studies suggest air pollution may contribute to disease development. It may also accelerate progression and trigger acute exacerbations.[1,23,24]

Several medical conditions are highly prevalent in IPF patients and may act as disease modifiers or contributors to pathogenesis through shared pathways. Gastroesophageal reflux disease (GERD) is present in up to 90% of IPF patients. The microaspiration theory posits that chronic, subclinical aspiration of gastric contents leads to repetitive low-grade injury to the distal lung epithelium. This perpetuates the cycle of injury and aberrant repair.[9,26] While a direct causal link remains difficult to prove, aggressive anti-reflux therapy is often employed in IPF management.[1,9,16,26]

Obstructive sleep apnea (OSA) is highly prevalent in the IPF population, partly due to shared risk factors such as obesity and male sex. OSA may contribute to disease progression through chronic intermittent hypoxia, increased oxidative stress, and sympathetic activation. These pathways can promote fibrotic processes and worsen pulmonary hypertension.[1,16,26]

Additionally, diabetes mellitus is more common in IPF patients than in the general population.[26,27] Hyperglycemia and insulin resistance can promote fibrosis through advanced glycation end-products (AGEs). These AGEs stimulate collagen cross-linking and activate pro-fibrotic signaling pathways. Diabetes is also associated with worse outcomes in IPF.[9,16,27]

Interstitial lung abnormalities (ILAs) are incidental radiographic findings on CT scans, characterized by non-dependent ground-glass or reticular abnormalities, architectural distortion, or traction bronchiectasis.[28] Fibrotic ILAs with features of early fibrosis are now recognized as a significant risk state. Individuals with fibrotic ILAs demonstrate a 5 to 10-fold increased risk of progressing to a clinical diagnosis of IPF over several years.[1,28,29] This

positions ILAs as a potential precursor stage or early manifestation in the IPF disease spectrum, offering a critical window for early intervention and monitoring.[28,29]

Figure 1 summarizes the main risk factors and contributors to IPF, categorized into demographic characteristics (male sex, older age), genetic predisposition (MUC5B variant, telomere-related mutations), behavioral and environmental exposures (cigarette smoking, air pollution, occupational dusts), associated health conditions (OSA, GERD, diabetes mellitus), and emerging clinical contexts (ILAs, post-COVID-19 pulmonary fibrosis).

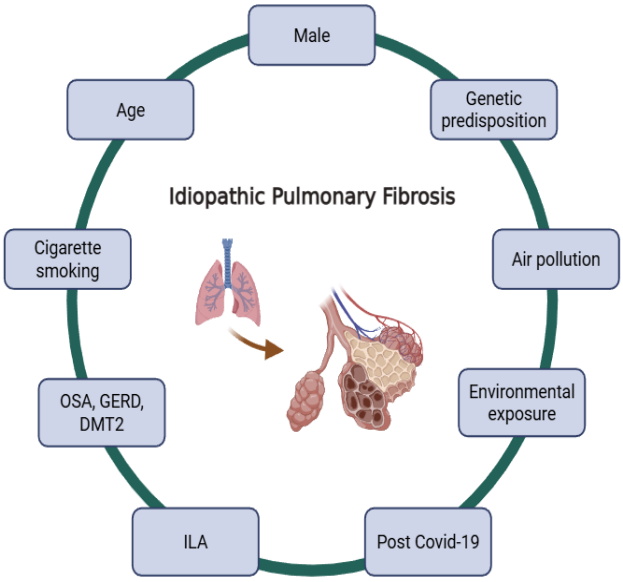

Figure 1. The main risk factors and contributors to IPF are categorized into key areas.

Post COVID-19 pulmonary fibrosis has emerged as a novel clinical concern. A subset of patients recovering from severe COVID-19 pneumonia develop persistent, progressive fibrotic lung changes.[9,26,30] While the natural history of this entity differs from classic IPF, it shares pathogenic features of severe epithelial injury and dysregulated repair. It remains to be seen whether COVID-19 acts as an inciting injury in genetically predisposed individuals to trigger classic IPF or represents a distinct post-infectious fibrotic entity.[30]

Pathogenesis

The pathogenesis of IPF represents a complex, self-perpetuating cycle of repetitive alveolar epithelial injury and dysregulated repair in a genetically susceptible host. This ultimately leads to the irreversible replacement of functional lung parenchyma with non-compliant scar tissue.[1,4,14] The pathogenic cascade is initiated by repetitive micro-injuries to the delicate alveolar epithelium, primarily targeting type I alveolar epithelial cells (AECs), which constitute over 95% of the alveolar surface.[4,14,16] Importantly, this pathogenic cascade does not remain confined to the lungs. The same fibrotic, inflammatory, and hypoxic mechanisms that destroy pulmonary architecture simultaneously create a vulnerable substrate for SVAs through systemic and cardiopulmonary pathways.[31,32]

In genetically predisposed individuals, cumulative exposures, including aging, cigarette smoke, environmental dusts, viral infections, and gastroesophageal reflux, overwhelm normal repair mechanisms. This leads to endoplasmic reticulum stress, mitochondrial dysfunction with elevated reactive oxygen species, impaired autophagy, and telomere attrition. These stressors drive alveolar epithelial cells, particularly progenitor type II AECs (AT2 cells), into premature senescence.[1,4,14,33]

Rather than undergoing apoptosis, senescent AT2 cells remain metabolically active and secrete a potent array of mediators known as the senescence-associated secretory phenotype (SASP).[33–35] Key SASP components include TGF-β1, PDGF, IL-1β, IL-6, CCL2, and various MMPs.[34] This SASP creates a persistent pro-fibrotic, pro-inflammatory microenvironment that promotes pathological repair.[35]

Critically, these SASP factors enter the systemic circulation and directly affect the heart. Circulating TGF-β1 and IL-6 promote atrial fibroblast proliferation and myocardial fibrosis, while TNF-α and reactive oxygen species alter cardiac ion channel function. This systemic spillover establishes a direct molecular link between lung fibrosis and atrial arrhythmogenesis.[1,34–36]

The SASP-rich microenvironment activates resident mesenchymal cells. Fibroblasts and pericytes proliferate and differentiate into activated myofibroblasts, characterized by α-smooth muscle actin expression and enhanced contractility.[4,34] These myofibroblasts are the principal effector cells

of fibrosis, responsible for excessive deposition of collagen types I and III, fibronectin, and tenascin-C.[33,35–37]

A critical pathogenic feature is myofibroblast apoptosis resistance. In normal wound healing, myofibroblasts undergo apoptosis once repair is complete.[4,34] In IPF, they persist due to aberrant pro-survival signaling (PI3K/Akt pathway) and impaired Fas-mediated apoptosis. This persistence is reinforced by a biomechanical positive feedback loop: stiffened ECM promotes further TGF-β1 activation and enhances myofibroblast survival, creating a self-sustaining cycle of fibrosis.[4,33–37]

The evolving ECM is not merely a passive scar but an active driver of disease progression. As fibrosis advances, the lung parenchyma stiffens dramatically, increasing mechanical stress on resident cells.[4,33] This stiffness is sensed via integrin-mediated mechanotransduction, activating YAP/TAZ, key regulators of pro-fibrotic gene expression.[36–38] Stiffened matrix also promotes latent TGF-β1 activation, providing constant stimulus for further fibroblast activation.[4,38–40] This vicious cycle explains IPF's relentless progression.[4,36–38]

Concurrent with parenchymal fibrosis, progressive obliteration of the pulmonary capillary bed and hypoxic vasoconstriction lead to elevated pulmonary vascular resistance. This imposes chronic pressure overload on the right ventricle (RV), causing RV hypertrophy and eventual dysfunction. Hemodynamic consequences transmit retrograde to the right atrium (RA), which experiences increased wall stress and dilation.[36,41]

Mechanical stretch of the RA activates stretch-activated ion channels, depolarizing the resting membrane potential and shortening action potential duration; both are pro-arrhythmic effects. Chronic stretch also induces transcriptional changes via mechanotransduction pathways (integrins and Rho/ROCK signaling), leading to patchy interstitial fibrosis in the atrial myocardium.[25,31,32,42] This fibrosis creates zones of conduction slowing and block adjacent to normal tissue, establishing conditions for re-entrant circuits underlying atrial flutter and fibrillation.[31,42]

While IPF is not a classic inflammatory disease, innate and adaptive immune dysregulation plays a modulatory role. Alternatively activated (M2) macrophages accumulate and secrete pro-fibrotic mediators (TGF-β1, PDGF).[4,33,34] Dendritic cells may promote a Th2/Th17-skewed response. Regulatory T cells (Tregs), though initially anti-inflammatory, may inhibit clearance of senescent cells. This altered immune landscape fails to suppress and may actively perpetuate the fibrotic response.[36–40]

Specific genetic variants establish the substrate for environmental factors. The MUC5B promoter variant (rs35705950) disrupts mucociliary clearance and host defense, promoting a pro-fibrotic microenvironment. Telomere-related gene mutations (TERT, TERC, RTEL1, and PARN) accelerate cellular senescence.[19,43] Surfactant protein gene mutations (SFTPC and SFTPA2) cause protein misfolding and ER stress in AT2 cells. These genetic lesions converge on epithelial cell dysfunction and senescence, priming the lung for fibrotic transformation.[1,4,33,35]

Chronic hypoxemia from impaired gas exchange has direct cardiac electrophysiological consequences. Cellular hypoxia depletes intracellular ATP, inhibiting the Na^+/K^+ ATPase pump. This leads to intracellular sodium and calcium accumulation via reverse-mode sodium-calcium exchange. Calcium overload promotes delayed and early afterdepolarizations, which can initiate focal atrial tachycardia and fibrillation.[36,41] At the tissue level, chronic hypoxemia stimulates carotid body chemoreceptors, leading to sustained sympathetic overactivity that shortens atrial refractory periods and promotes repolarization heterogeneity.[31,32,42] These hypoxic mechanisms operate independently of structural remodeling, providing a functional arrhythmogenic trigger even before overt cardiac structural changes develop.

Collectively, these pulmonary pathogenic mechanisms-senescence-driven inflammation, pulmonary vascular remodeling, and chronic hypoxemia-do not operate in isolation. They create a systemic environment that promotes right atrial structural remodeling, electrical instability, and

sympathetic activation.[31,32,42] The pathways detailed above mechanical stretch from pulmonary hypertension, cellular calcium dysregulation from hypoxia, and circulating pro-inflammatory cytokines establish a mechanistic foundation for elevated SVA risk in IPF.

Clinical Presentation

Idiopathic pulmonary fibrosis typically manifests with an insidious onset of progressive respiratory symptoms. Chief among these are exertional dyspnea and a persistent, non-productive cough, which gradually worsen over months to years.[1,2] Physical examination is often notable for bibasilar, "Velcro-like" inspiratory crackles, an auditory hallmark of underlying fibrosis. As the disease progresses, exercise tolerance declines, accompanied by worsening hypoxemia.[9,34]

Pulmonary function tests consistently reveal a restrictive ventilatory defect, characterized by reduced lung volumes and a disproportionately severe impairment in diffusing capacity for carbon monoxide (DLCO), indicative of compromised gas exchange.[1,9] The identification of ILA on thoracic imaging, especially in those with a fibrotic pattern, warrants thorough clinical assessment. These findings may represent early or subclinical IPF and necessitate careful longitudinal monitoring.[28,29]

Patients with IPF and concurrent SVAs may present with palpitations, episodic dizziness, lightheadedness, or near-syncope. In more severe cases, the onset of atrial fibrillation or atrial flutter can precipitate acute decompensation, manifesting as sudden worsening of dyspnea, chest discomfort, or overt syncope.[5,41] Hemodynamic vulnerability. The loss of atrial "kick" (atrial contraction contributing to ventricular filling) during SVAs can significantly compromise cardiac output in IPF patients, who are often preload-dependent due to right ventricular dysfunction from pulmonary hypertension.[5,41] This hemodynamic vulnerability means that even well-tolerated SVAs in otherwise healthy individuals may cause severe symptoms or acute respiratory failure in the IPF population.

Physical examination findings that raise suspicion for underlying SVAs include an irregularly irregular pulse (suggesting atrial fibrillation), tachycardia out of proportion to the degree of respiratory compromise, or jugular venous distention with prominent a-waves (suggesting tricuspid regurgitation or right atrial pressure elevation).[5,41] Electrocardiographic (ECG) findings may reveal the absence of P waves, irregular RR intervals, or other features diagnostic of atrial fibrillation, atrial flutter, or supraventricular tachycardia.

Diagnosis

The diagnostic evaluation for IPF, as refined in the 2022 ATS/ERS/JRS/ALAT guidelines, requires comprehensive exclusion of alternative causes of ILD before a definitive diagnosis can be established.[1,2] This process includes ruling out connective tissue diseases, environmental or occupational exposures, medication-induced lung injury, and fibrotic hypersensitivity pneumonitis.[1,2,26]

Initial assessment includes a structured history (family history, medication review, and investigation of potential environmental exposures) and physical examination to identify signs of underlying systemic illness.[1,2,44,45] Serologic testing helps exclude autoimmune etiologies. A basic panel typically includes antinuclear antibodies, rheumatoid factor, anti-CCP antibodies, and C-reactive protein. When findings suggest an autoimmune disorder, rheumatology referral is indicated for multidisciplinary discussion.[2,44,45]

High-resolution computed tomography is a cornerstone of the diagnostic evaluation for suspected IPF. A confident diagnosis can often be made without surgical biopsy when HRCT demonstrates a definite or probable usual interstitial pneumonia (UIP) pattern in the appropriate clinical context. A definite UIP pattern is defined by subpleural and basal-predominant fibrosis with heterogeneous distribution, featuring honeycombing, a key prognostic indicator with or without traction bronchiectasis.[1,2,26]

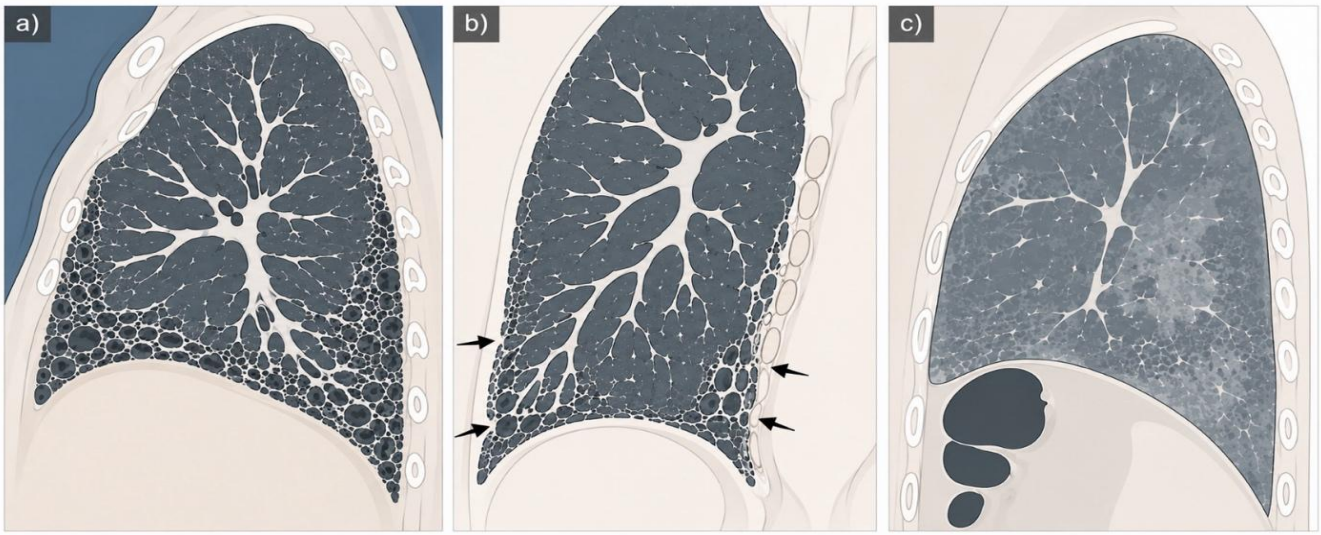

Figure 2. a) Sagittal HRCT image of the right lung showing a definite UIP pattern; b) Coronal HRCT image (magnified view of the right lung) showing a probable UIP pattern; c) Sagittal HRCT image of the left lung illustrating an indeterminate UIP pattern

Figure 2 illustrates the spectrum of UIP patterns on HRCT. Panel (a) shows a definite UIP pattern with subpleural predominant, lower-lung predominant reticular abnormality, honeycombing, and traction bronchiolectasis. Panel (b) demonstrates a probable UIP pattern with peripheral lung infiltration and numerous traction bronchiolectases (arrows) in the subpleural lung parenchyma of the right lower lobe. Panel (c) shows an indeterminate UIP pattern with heterogeneous subpleural lung infiltration composed predominantly of ground-glass opacities of varying attenuation. These imaging patterns guide clinicians along a diagnostic pathway, as both definite and probable UIP patterns have high positive predictive value for histologic UIP.[1,2,26]

Given the elevated SVA risk in IPF, diagnostic evaluation should extend beyond pulmonary assessment. Although current guidelines do not mandate routine cardiac screening, baseline ECG and Holter monitoring are reasonable in patients with advanced disease, severe hypoxemia, or right heart strain signs.[5,41]

Echocardiography is recommended in the initial IPF workup to assess for pulmonary hypertension, RV dysfunction, and RA enlargement; all independent SVA risk factors.[5,41] Elevated pulmonary artery pressure, RA dilation, or tricuspid regurgitation should alert clinicians to heightened arrhythmia risk and prompt closer rhythm monitoring.[5,41]

When HRCT shows an indeterminate or atypical UIP pattern, additional diagnostics may be warranted. Bronchoalveolar lavage (BAL) helps exclude alternative diagnoses: marked lymphocytosis (>30–40%) suggests chronic hypersensitivity pneumonitis or sarcoidosis; neutrophilic or eosinophilic predominance supports other conditions.[1,2] For histopathological confirmation, transbronchial lung cryobiopsy (TBLC) is an acceptable, safer alternative to surgical lung biopsy in experienced centers, with a diagnostic yield for UIP of 70–80%. The choice depends on local expertise, patient comorbidities, and the diagnostic question.[1,2,46]

In summary, while IPF diagnosis focuses on parenchymal lung disease, clinicians should remain vigilant for cardiovascular complications. Early recognition of subclinical pulmonary hypertension, RA enlargement, or right heart strain should prompt baseline ECG and longitudinal rhythm monitoring to facilitate early SVA detection and management.

Management

The contemporary management of IPF requires a multimodal strategy that addresses not only disease progression but also associated cardiovascular complications, particularly SVAs. While antifibrotic therapies slow lung function decline, comprehensive management — including correction of hypoxemia, treatment of pulmonary

hypertension, optimization of comorbidities, and appropriate arrhythmia management — may reduce SVA risk and improve outcomes.[1,2]

Two antifibrotic agents, pirfenidone and nintedanib, slow disease progression in IPF. Pirfenidone inhibits TGF-β1 synthesis and signaling, while nintedanib targets multiple tyrosine kinases, including VEGFR, PDGFR, and FGFR.[1,2,16] Pirfenidone has also been associated with a lower risk of acute exacerbations of IPF, critical events carrying high mortality.[16,44] Both agents reduce the annual rate of forced vital capacity decline by approximately 50% compared to placebo.[47,48]

Importantly, while these agents modify pulmonary fibrosis, neither has been specifically studied for arrhythmia prevention in IPF. By slowing disease progression and potentially reducing the rate of pulmonary hypertension development, antifibrotic therapy may indirectly lower cumulative exposure to arrhythmogenic substrates. However, no current evidence supports the use of antifibrotics as primary or secondary prevention for SVAs.

Pulmonary hypertension affects 30–50% of patients with advanced IPF and is a powerful predictor of SVA risk through RA stretch and structural remodeling. While targeted pulmonary hypertension therapies (e.g., phosphodiesterase-5 inhibitors, endothelin receptor antagonists) have not demonstrated consistent benefits in IPF-related pulmonary hypertension and are not routinely recommended, management focuses on treating underlying hypoxemia and optimizing fluid status.[5,36,41]

Diuretics play an important role in IPF patients with pulmonary hypertension and right heart failure. By reducing RA pressure and wall stress, judicious diuretic use may decrease atrial stretch, a direct trigger for arrhythmias. However, excessive diuresis can reduce preload and compromise cardiac output, particularly in preload-dependent patients. Therefore, careful fluid management with monitoring of renal function and electrolytes is essential, as electrolyte disturbances (particularly hypokalemia and hypomagnesemia) can further increase arrhythmia susceptibility. [5,36,41]

Rate control medications (beta-blockers and calcium channel blockers) should be used cautiously in patients with documented SVAs and concomitant pulmonary hypertension. Beta-blockers may be beneficial for rate control in atrial fibrillation but theoretically could worsen pulmonary vasoconstriction. Non-dihydropyridine calcium channel blockers (verapamil, diltiazem) are generally avoided in pulmonary hypertension due to negative inotropic effects. Multidisciplinary management involving pulmonologists and cardiologists is strongly recommended for complex cases [5,36,41]

Chronic hypoxemia is a major driver of arrhythmogenesis in IPF through multiple mechanisms: calcium handling abnormalities, sympathetic activation, and promotion of pulmonary vasoconstriction.[1,2,49] Therefore, correction of hypoxemia represents a potentially modifiable target for SVA risk reduction. Long-term oxygen therapy is indicated for IPF patients with significant resting hypoxemia (PaO_2 ≤55 mmHg or SpO_2 ≤88%) or exertional desaturation. Ambulatory oxygen should be provided to correct exertional hypoxemia, as it has been shown to improve exercise tolerance and reduce dyspnea. The goal is to maintain oxygen saturation ≥90% during rest, sleep, and exertion[1,2,49]

Structured pulmonary rehabilitation programs involving supervised exercise training, education, and psychosocial support provide demonstrable benefits in improving exercise capacity, reducing dyspnea perception, enhancing peripheral muscle strength, and improving health-related quality of life.[1,2,49] These benefits persist for several months post-program, and maintenance exercise is encouraged. Pulmonary rehabilitation is recommended for all suitable IPF patients regardless of disease severity.[1]

The systematic management of associated comorbidities is equally critical, as these conditions frequently exacerbate symptoms and contribute to poorer clinical outcomes. For GERD, aggressive acid suppression with proton pump inhibitors is commonly used in IPF management and may theoretically reduce arrhythmia, though this has not been specifically studied.[1,2,49] Screening for OSA with

appropriate polysomnography and treatment with continuous positive airway pressure may reduce arrhythmia burden, although prospective studies in IPF are lacking. Hyperglycemia promotes atrial fibrosis and electrical remodeling. Strict glycemic control should be pursued, as hyperglycemia is a modifiable risk factor for atrial fibrillation in other populations and likely in IPF as well.[1,2,49]

For appropriate candidates with advanced disease, lung transplantation remains the only intervention capable of significantly improving long-term survival.[1,16] The therapeutic pipeline is active, with research focused on novel pathways: agents targeting cellular senescence (senolytics), specific matrix components (e.g., lysyl oxidase-like 2 inhibitors), autophagy, Wnt/β-catenin signaling, and biologic agents against specific cytokines. The goal remains to move beyond slowing decline to achieving disease stabilization or even fibrosis regression.[1,50]

Ongoing research is needed to determine whether systematic SVA screening improves outcomes in IPF, whether specific antiarrhythmic strategies are more effective in this population, and whether aggressive management of hypoxemia, pulmonary hypertension, and comorbidities reduces incident arrhythmias. Until then, clinical vigilance and proactive management remain the cornerstones of reducing SVA-related morbidity and mortality in IPF.

THE PATHOPHYSIOLOGICAL PATHWAYS LINKING IDIOPATHIC PULMONARY FIBROSIS TO SUPRAVENTRICULAR ARRHYTHMIAS

Idiopathic pulmonary fibrosis is not merely a lung disease but a systemic cardiopulmonary syndrome. Progressive pulmonary fibrosis directly remodels cardiac structure and function, creating a highly vulnerable substrate for electrical instability. This intricate connection is mediated through three interdependent pathological pathways: mechanical stress from pulmonary hypertension, chronic hypoxemia, and systemic inflammation.[17,41,51,52]

Supraventricular arrhythmias encompass abnormal cardiac rhythms originating from the sinoatrial node, atria, atrioventricular node, or proximal bundle of His.[5] The fundamental mechanisms underlying SVAs involve abnormal impulse initiation through enhanced automaticity or triggered activity, and abnormal impulse conduction via re-entrant circuits, which are potentiated by structural alterations such as atrial fibrosis, chamber dilation, inflammatory states, and autonomic tone shifts.[5,41,53] This electrophysiological foundation is crucial for understanding how the pathological changes induced by IPF create an environment ripe for arrhythmogenesis.

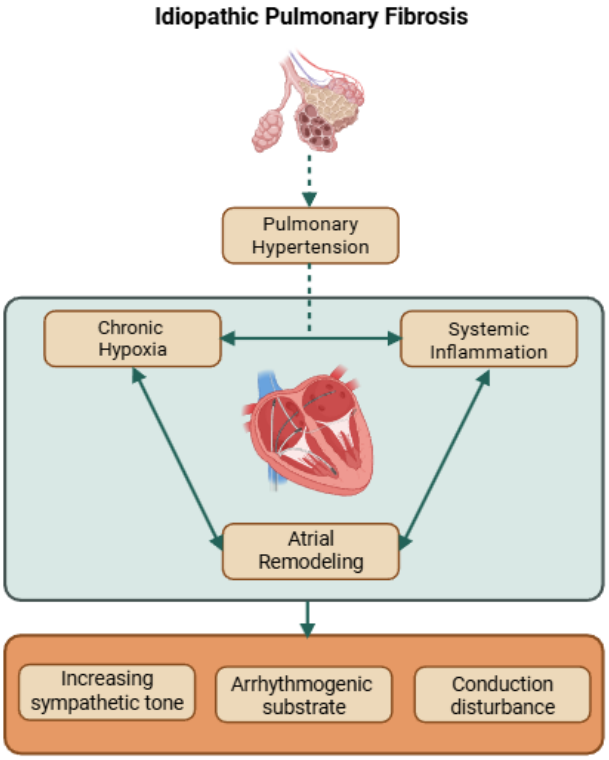

Figure 3. Pathophysiological triad linking IPF to SVA

Figure 3 provides a visual summary of this pathophysiological triad. As illustrated, IPF promotes pulmonary hypertension, chronic hypoxemia, and systemic inflammation, which collectively drive right atrial remodeling. This remodeling establishes an arrhythmogenic substrate characterized by conduction disturbances and heightened sympathetic tone, ultimately increasing susceptibility to atrial fibrillation and flutter. The following subsections examine each pathway in detail.

The Mechanical Pathway: Pulmonary Hypertension and Right Atrial Remodeling

The most direct link between IPF and SVAs is group 3 pulmonary hypertension due to lung disease

and/or hypoxia, affecting 30–50% of patients with advanced IPF.[16,41,54] Progressive fibrosis and hypoxic vasoconstriction obliterate the pulmonary capillary bed, elevating pulmonary vascular resistance. This condition imposes chronic pressure overload on the RV, causing compensatory RV hypertrophy and eventual dysfunction. Hemodynamic consequences transmit retrograde to the RA, which experiences increased wall stress and dilation.[16,52,55]

Mechanical stretch directly alters ion channel function, promoting triggered activity and early afterdepolarizations. Chronic stretch activates mechanotransduction pathways (integrins and Rho/ROCK signaling), inducing maladaptive hypertrophy and interstitial fibrosis. Collectively, these mechanisms create a vulnerable arrhythmogenic substrate characterized by conduction slowing, heterogeneous repolarization, and increased susceptibility to re-entrant circuits.[41,56]

Patchy interstitial fibrosis with collagen type I and III deposits disrupts normal myocardial architecture. This creates microscopic zones of conduction slowing and block adjacent to normal tissue, establishing conditions for macro re-entrant circuits underlying atrial flutter and multiple wavelet re-entry characteristic of atrial fibrillation.[16,41,52] At the ultrastructural level, mechanical stress downregulates connexin 43 and 40 gap junctions, impairing cell-to-cell coupling. Electrical impulses follow tortuous "zigzag" pathways through fibrotic tissue, resulting in fractionated electrograms and increased refractory period dispersion.[41,52]

Even borderline pulmonary artery pressure elevation (mean PAP 21–24 mmHg), previously considered insignificant, is now recognized as a potent predictor of arrhythmia and mortality in IPF, underscoring the continuum of risk below traditional pulmonary hypertension diagnostic thresholds.[16,41,54]

The Hypoxic Pathway: Cellular Instability and Autonomic Dysregulation

Concurrent with mechanical stress, chronic hypoxemia from impaired gas exchange creates a second major arrhythmogenic pathway. Cellular hypoxia depletes intracellular ATP, inhibiting the Na^{+}/K^{+} ATPase pump. This leads to intracellular sodium and calcium accumulation via reverse-mode sodium-calcium exchange.[17,41,55] Calcium overload promotes delayed and early afterdepolarizations that can initiate focal atrial tachycardia and fibrillation.[16,41,54]

Chronic hypoxemia stimulates carotid body chemoreceptors, leading to sustained sympathetic overactivity with elevated circulating catecholamines. This increases resting heart rate, shortens atrial refractory periods via beta-adrenergic receptor activation, and promotes repolarization heterogeneity. Hypoxia-induced downregulation of cardiac muscarinic receptors further reduces parasympathetic influence.[41,42,54]

The pulmonary veins, particularly myocardial sleeves extending from the left atrium, contain pacemaker-like cells with spontaneous phase 4 depolarization. These regions are highly sensitive to hypoxic stimuli, which can directly induce ectopic firing through hypoxia-inducible factor-1α (HIF-1α)-mediated changes in ion channel expression, serving as critical triggers for atrial fibrillation initiation.[41,42,54]

Mitochondrial dysfunction from chronic hypoxia generates reactive oxygen species that modify ion channel function through oxidation of critical cysteine residues, particularly affecting ryanodine receptors in the sarcoplasmic reticulum, promoting calcium leak, and further triggering activity.[41,52]

The Inflammatory Pathway: The Systemic Profibrotic Milieu

The third critical pathway involves the persistent, low-grade systemic inflammatory state characteristic of IPF, marked by elevated circulating levels of IL-6, TNF-α, CRP, and TGF-β1. These inflammatory mediators directly alter cardiac ion channel function, slowing conduction velocity and promoting re-entry.[4,33,54]

At the structural level, these cytokines stimulate atrial fibroblast proliferation and extracellular matrix deposition, accelerating the fibrotic substrate for arrhythmias. Thus, systemic inflammation contributes to SVAs through both functional (ion channel) and structural (fibrosis)

mechanisms.[17,41,55]

Inflammatory mediators directly affect the cardiac autonomic nervous system through cytokine receptors expressed on cardiac ganglia and nerve terminals, promoting sympathetic predominance and vagal withdrawal. This is particularly significant given the dense autonomic innervation of the pulmonary veins and left atrium regions critically involved in arrhythmia initiation.[4,41]

Several unique features explain the left atrium's susceptibility to inflammation-induced arrhythmogenesis. First, myocardial sleeves extending into the pulmonary veins contain pacemaker-like cells that develop abnormal automaticity under inflammatory conditions (elevated IL-6, TNF-α, and oxidative stress), serving as ectopic drivers of atrial fibrillation. Second, pulmonary vein ostia are richly innervated by ganglionated plexi; inflammatory activation promotes sympathetic discharge while suppressing parasympathetic tone, creating a pro-arrhythmic autonomic imbalance.[17,41,42]

Third, the left atrium's complex geometry; variable wall thickness and multiple structures provide an ideal substrate for micro-reentry, particularly when inflammatory cytokines (notably TGF-β1) promote preferential fibrosis in these regions. Thus, the left atrium and pulmonary veins are active participants in SVA pathogenesis in IPF, not passive bystanders.[17,41,42]

These three pathways, mechanical stress from pulmonary hypertension, chronic hypoxemia, and systemic inflammation, synergistically interact to create what can be termed the "IPF arrhythmogenic triad".[17,41] Those with advanced age, severely reduced DLCO (<40% predicted), and evidence of pulmonary hypertension or RV dysfunction represent the highest-risk phenotype warranting vigilant rhythm monitoring, as even asymptomatic arrhythmias may have significant hemodynamic consequences in this preload-dependent population.

The development of an SVA in IPF is not merely a comorbidity but a marker of advanced cardiopulmonary disease and a direct contributor to mortality, often precipitating acute decompensation through loss of atrial kick, increased ventricular rates, and worsening right heart failure, establishing a vicious cycle where arrhythmia worsens hemodynamics, which in turn promotes further arrhythmia.[32,41]

CONCLUSION

The convergence of IPF and SVAs represents a critical clinical entity with profound prognostic implications. This review delineates three interdependent pathways: pulmonary hypertension, chronic hypoxemia, and systemic inflammation that culminate in right atrial remodeling and an arrhythmogenic cardiac substrate.SVA onset in IPF is not incidental but a marker of advanced disease and a catalyst for deterioration. Clinicians should recognize high-risk patients (advanced disease, severe hypoxemia, pulmonary hypertension or RV dysfunction) and maintain a low threshold for cardiac monitoring.

Current evidence is largely observational and retrospective. No RCTs have evaluated antiarrhythmic strategies in IPF, and no guidelines exist for SVA screening or management in this population. Prospective studies and RCTs are needed to: (1) confirm the IPF–SVA relationship, (2) determine if systematic screening improves outcomes, (3) evaluate antiarrhythmic strategies, and (4) establish evidence-based guidelines. Proactive, multidisciplinary management guided by clinical judgement remains reasonable. Current evidence does not support universal screening but mandates clinical vigilance in high-risk patients.

CONFLICT OF INTEREST

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