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LITERATURE REVIEW: CARDIAC COMPLICATION OF IDIOPATHIC PULMONARY FIBROSIS

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Abstract: Cardiac complication of idiopathic pulmonary fibrosis. *Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial pneumonia of unknown cause that is associated with radiological and histologic features of usual interstitial pneumonia (UIP). Idiopathic pulmonary fibrosis occurs primarily in adult and associated with poor prognosis with patients typically survive 2-3 years after diagnosis, although some cases progress much faster than others. Symptoms of IPF include cough and shortness of breath, especially during activity. In severe cases, respiratory failure may occur. IPF is often linked to several health problems, including lung cancer, sleep apnea, heart disease, and digestive issues like acid reflux. The cardiovascular problem related to IPF are pulmonary hypertension, coronary artery disease, arrythmia, and iatrogenic disease caused by IPF pharmacological treatment. This literature review will explain the link between IPF and its pathogenesis in causing cardiac complications based on available literature.*
Keywords: *Arrythmia, Coronary Artery Disease, Idiopathic Pulmonary Fibrosis, Pulmonary Hypertension*

Abstrak: Gangguan jantung pada *idiopathic pulmonary fibrosis.* *Idiopathic pulmonary fibrosis* (IPF) adalah penyakit yang ditandai dengan fibrosis kronik pada jaringan interstitial paru tanpa sebab yang diketahui secara jelas dan berkaitan dengan gambaran radiologis dan histologis yang disebut dengan *usual interstitial pneumonia* (UIP). Penyakit ini terutama terjadi pada orang dewasa dan memiliki prognosis yang buruk. Pasien IPF umumnya bertahan hidup selama 2-3 tahun setelah diagnosis ditegakkan, namun beberapa kasus memburuk jauh lebih cepat. Gejala IPF meliputi batuk dan sesak napas, terutama saat beraktivitas. Pada kasus yang parah, kegagalan pernapasan dapat terjadi. *Idiopathic pulmonary fibrosis* terkait dengan berbagai masalah kesehatan, termasuk kanker paru, *sleep apnea*, penyakit jantung, dan masalah pencernaan seperti *gastroesophageal reflux disease*. Masalah kardiovaskular yang terkait dengan IPF mencakup hipertensi pulmonal, penyakit arteri koroner, aritmia, dan penyakit iatrogenik yang disebabkan oleh terapi farmakologis IPF. Tinjauan literatur ini akan menjelaskan hubungan antara IPF dan komplikasi jantung yang dapat disebabkan berdasarkan literatur yang tersedia.
Kata Kunci: Aritmia, Hipertensi Pulmonar, *Idiopathic Pulmonary Fibrosis*, Penyakit Jantung Koroner

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial pneumonia of unknown cause that is associated with radiological and histologic features of usual interstitial pneumonia (UIP) (Raghu et al., 2022). Idiopathic pulmonary fibrosis occurs primarily in adult and associated with poor prognosis with patients typically survive 2-3 years after diagnosis, although some cases progress much faster than others. It's a relatively uncommon disease, with prevalence of

14-43 out of every 100,000 people. However, it's becoming more prevalent today due to better detection methods and an aging population (Agrawal et al., 2016). Symptoms of IPF include cough and shortness of breath, especially during activity. In severe cases, respiratory failure may occur. Clinicans diagnose IPF based on a combination of examination, including "Velcro" like rales and clubbing finger on physical exam, specific pattern on thoracic CT-scan patterns, and histopathology of lung tissue samples. Idiopathic pulmonary fibrosis is an exclusion disease, it can only be diagnosed when other differential diagnosis has been excluded (Agrawal et al., 2016). IPF is often linked to several health problems, including lung cancer, sleep apnea, heart disease, and digestive issues like acid reflux. The cardiovascular problem related to IPF are pulmonary hypertension, coronary artery diseaes, heart failure, arrythmia, and iatrogenic disease caused by IPF pharmacological treatment. This article will explore the link between IPF and heart problems (Agrawal et al., 2016).

METHODS

This literature review was written using literature published within the last 20 years. The literature review was written by pulmonologists, immunologist, and cardiologist with years of experience. Literature was chosen by the expertise of the authors. No systematic review is done due to time constraints.

RESULTS

Pathogenesis and patophysiology of IPF

The exact etiology of IPF is still unknown, hence the term "idiopathic", however recent advances describing specific clinical and pathologic features of IPF have led to better understanding of the molecular pathways that are pathologically activated in the disease. The sequence of events that may lead to the development of IPF can be divided into three patophysiologic stages which are predisposition, initiation, and progression.(Wolters, Collard & Jones, 2014) (Figure 1)

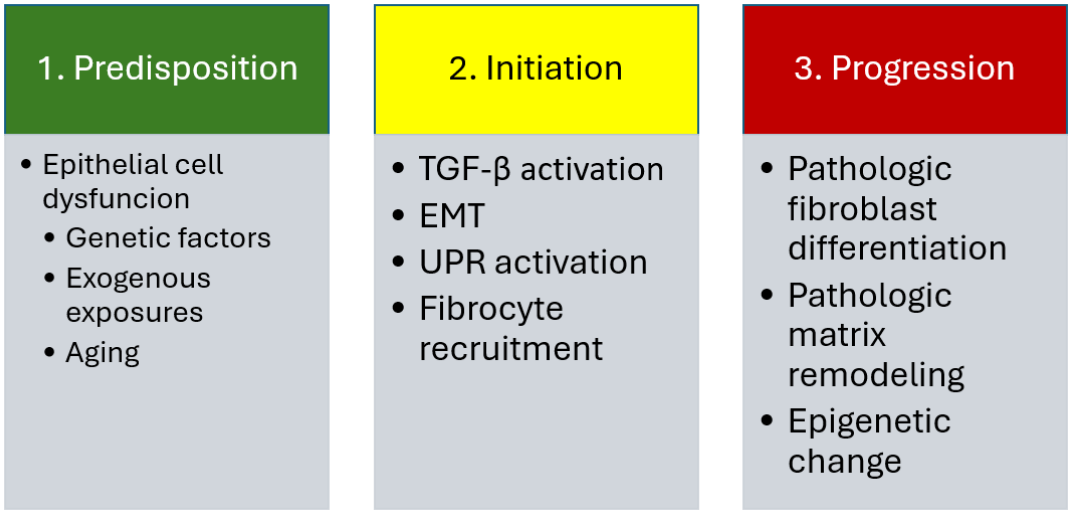

Figure 1. Pathophysiologic stages of idiopathic pulmonary fibrosis (IPF). Adapted from Wolter, et al *(Wolters, Collard & Jones, 2014)*.

Predisposition stage include predisposing factors that increase the risk of patients having IPF. This predisposing factors include genetic mutation or variations and environmental exposures. For example, the single nucleotide polymorphism (SNP) rs 35705950 of MUC5B gene is associated with IPF. This SNP of MUC5B causes MUC5B to be expressed 37.4 times higher compared to unaffected subject. The MUC5B SNP can be detected in 34% patient with IPF compared to only 11% of healthy control. Another

mutation in the gene called SPC gene, which encode surfactant protein C, and TERT/TERC, which regulate telomerase and associated with aging process, are also associated with IPF. The exact mechanism of how these mutation cause IPF is still unknown but believed to be associated with alveolar epithelial dysfunction. Another predisposing factors worth mentioning is exogenous exposure and aging. Environmental stressess such as exposure to tobacco smoke and pollutant can cause epigenetic changes that contribute to the increased risk of IPF. Aging also plays important role with most of patients diagnosed with IPF are above 50 years old. These three factors ultimately lead to epithelial cell dysfunction which predispose individuals to IPF (Wolters, Collard & Jones, 2014).

In the initiation stage, molecular pathway associated with epithelial dysfunction contribute to the formation of IPF. Studies found that the activity of transforming growth factor β (TGF- β) is increased in the IPF patient's lung. The possible mechanisme of increased TGF- β in causing IPF is by inhibiting proliferation of alveolar epithelial cell, differentiate fibroblast to myofibroblast, and promotes mesenchymal transition of epithelial cells. It is possible that in IPF, fibroblasts are derived from epithelial cells through process called epithelial-mesenchymal transition (EMT) (Wolters, Collard & Jones, 2014).

Another process that contribute in initiation stage is a process called endoplasmic reticulum stress (ER stress). Endoplasmic reticulum is an organelle where secreted and membrane proteins are made, folded, and matured. The protein then packaged and transported by the Golgi complex. The ER stress happens when there is an imbalance between the demand for protein synthesis and the its capacity to synthesize the required protein. The ER stress activates unfolded protein response (UPR) and activates various biochemical pathway designed to match the production capacity demanded by body. If the UPR cannot match the demand, the cell enter apopototic pathway. Moreover, UPR activation also associated with increased TGF- β and EMT activity further contributing to the fibrosis.(Wolters, Collard & Jones, 2014) In the final progression stage, differentiation of fibroblast, deposition and remodelling of abnormal quantity of extracellular matrix, and epigenetic change within fibroblast and epithelial cell directly cause fibrosis, remodel lung tissue, and increase the stiffness of lung tissue (Wolters, Collard & Jones, 2014).

Clinical and Radiological Features of IPF

The most common clinical manifestation of IPF is dyspnea. The severity of dyspnea correlate well with the quality of life and survival of IPF patients. Other common symptoms is cough which more prevalent in IPF patient with more advanced disease. Cough is believed to be an independent predictor of IPF progression. Severity of cough is significantly associated with the presence of MUC5B polymorphism (Scholand et al., 2014). In physical examinaton, fine late inspiratory crackles, often described as "velcro"-like can commonly be heard on lower posterior lung zones auscultation. Clubbing fingers indicative of chronic hypoxia is found on 30-50% of patient with IPF. The presence of clubbing fingers is correlated with the extend of fibrosis in the lung (Nakamura & Suda, 2015).

Spirometry often shows decrease in lung volume and diffusion capacity. More than 75% of patient with IPV have decreased total lung capacity and more than 50% have decreased forced vital capacity (FVC). As the disease progress, the rasio of forced expiratory volume in one second/FVC increases caused by the decrease in FVC and normal FEV1. The diffusing capacity for carbon monoxide (DLCO) decreases. The spirometry should be done routinely to monitor the progression of IPF. Declines in lung function, especially in FEV1 >10% and DLCO >15% predict higher mortality in IPF patient (Zappala et al., 2010).

The hallmark radiological pattern of IPF are usual interstitial pneumonia (UIP)

pattern. The UIP pattern is a set of characteristic that can be found in high resolution computed tomography (HRCT) scan of the thorax. The UIP pattern consist of features and distribution of lesion. In UIP pattern, the features that can be found are honeycombing with or without traction bronchiectasis. The distribution is subpleural and basal-dominant. There should be an absence or very mild presence of other features such as ground glass opacification. Example of UIP pattern can be seen in figure 2. If one criteria is not met, for example GGO is present, the lesion can also be found in the apex, or reticular opacities is found instead of honeycombing, then the pattern is called probable UIP (Raghu et al., 2022) (figure 3). If the distribution is diffuse without subpleural dominance and the features does not suggest any specific etiology but no alternative diagnosis is found, it may be classified as indeterminate UIP. Alternative diagnosis must be sought if the features, distribution, pattern are consistent with another type of interstitial lung disease, for example peribronchovascular predominant with subpleural sparing often seen in nonspecific interstitial pneumonia (NSIP) (Raghu et al., 2022).

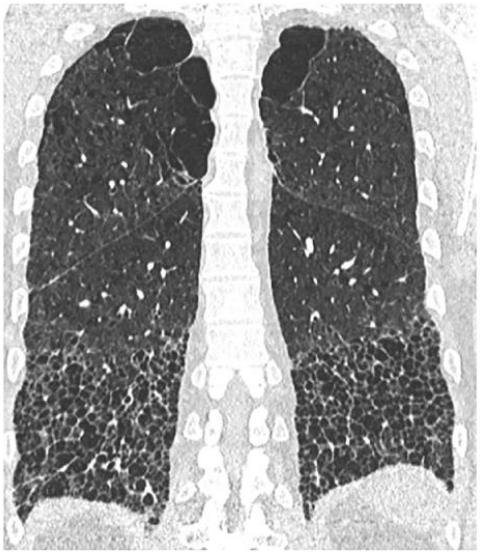

Figure 2. Usual interstitial pneumonia pattern. Note the honeycombing features and subpleural basal-dominant distribution (Raghu et al., 2022).

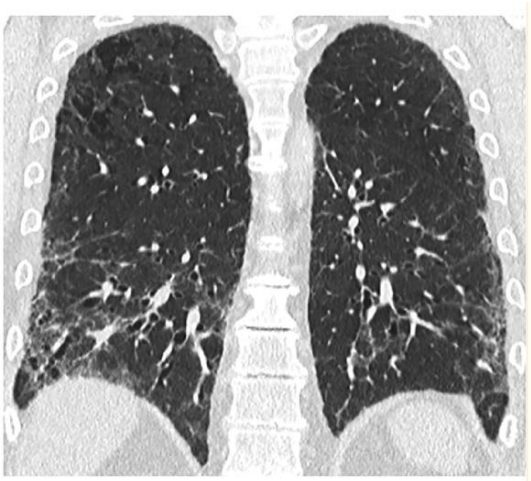

Figure 3. Probable UIP pattern. Note the subpleural basal distribution with reticular opacities and GGO on the base of the lungs *(Raghu et al., 2022).*

Idiopathic pulmonary fibrosis is a diagnosis of exclusion. Other possible causes should be excluded first, for example ILD caused by rheumatoid disease or exposure to environmental hazard. After excluding other etiology, it is recommended that IPF be diagnosed through multidisciplinary discussions consisted of respiratory clinician, radiologist, and pathologist (Raghu et al., 2022).

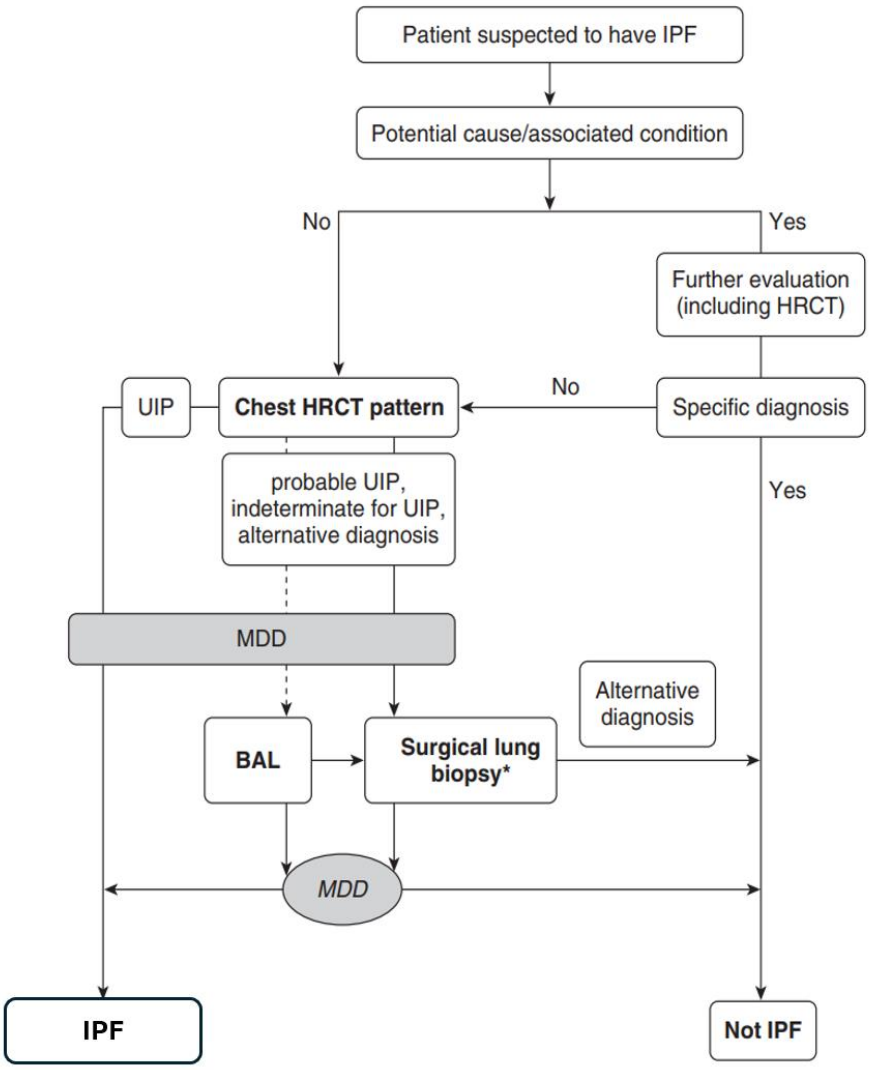

Figure 4. Algorithm for diagnosing IPF. Other diagnosis should be ruled out before diagnosing IPF. MDD: multidiscplinary discussion (Raghu et al., 2022).

Idiopathic Pulmonary Fibrosis and pulmonary hypertension

Pulmonary hypertension (PH) is a complication of IPF. It contribute significantly to the mortality and morbidity of patient with IPF. Pulmonary hypertension is defined as increased mean pulmonary artery pressure (mPAP) >20 mmHg. According to published guidelines by American Heart Association, pulmonary hypertension can be classified into five categories according to its underlying cause, which are pulmonary arterial hypertension, pulmonary hypertension due to left heart disease, pulmonary hypertension associated with lung disease, pulmonary hypertension associated with pulmonary

artery obstructions, pulmonary hypertension due to unknown cause. Pulmonary hypertension in IPF belongs to group 3, PH associated with lung disease (Maron, 2023).

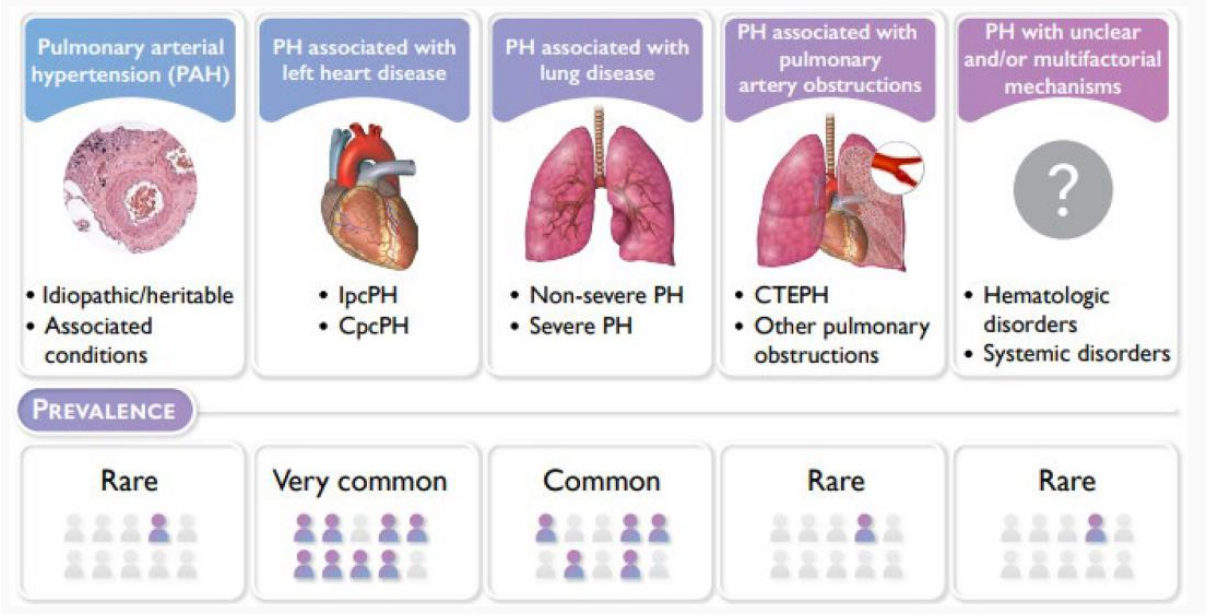

Figure 5. Five categories of pulmonary hypertension according to its underlying cause (Maron, 2023).

Estimating the prevalence of PH in IPF proves arduous due to several factors. First, IPF typically manifests insidiously making it often eluding early diagnosis and potentially skewing the apparent incidence of PH toward overestimation among affected individuals. Pulmonary hypertension typically only develop in the later stage of IPF while the early stage of IPF often gives mild symptoms only. Second, echocardiograms, a common diagnostic tool, might be unreliable for PH-IPF. Right heart catheterization (RHC), the gold standard, is invasive and impractical for large-scale studies. Finally, most PH-IPF data comes from small groups of patients seeking lung transplants, not representing the entire IPF population. Study done by Lettieri et al done in group of patients planned to undergo lung transplantation found that 32% of patients have PH diagnosed by RHC. Another study by Patel, et al found that 22% of patients with IPF have PH. However, we have to note that these groups were patients in late stage of IPF having lung transplantation (Lettieri et al., 2006; Patel et al., 2007). Another study called ARTEMIS-IPF trial, which excluded very sick patients, offered a unique perspective. Here, only 10% had PH at the outset, suggesting a lower prevalence in milder IPF. Furthermore, only 5% developed PH during follow-up, indicating slow progression in this group. Based on these studies we can conclude that the prevalence of PH among IPF patients ranging between 10% in early IPF to 32% in late stage IPF (Agrawal et al., 2016; Raghu, 2013).

Idiopathic pulmonary fibrosis causes damage to pulmonary blood vessels through several mechanisms. The central component in hypoxic pulmonary hypertension is the hypoxia inducible factors (HIF). Hypoxia inducible factors are protein molecules that act as cellular messengers. In hypoxic environment, HIF induce inflammation and activate signaling pathways in pulmonary arterial endothelial cells (PAECs) and pulmonary artery smooth muscle cells. Activation of HIF promotes aggregation of inflammatory cells and release of inflammatory mediators. The known effects of HIV are increasing macrophage proliferation, chemotaxis, and infiltration, drive the release of cytokines, increase reactive oxygen

species (ROS) production, increase neutrophil survival, and triggering NF-kB pathway. The activation of NF-kB pathway boost the vascular endhotelial growth factors (VEGF) (Ye, Xu & Wuren, 2023). Ultimately through this processes, chronic hypoxia causes hypertrophy of smooth muscle cells and collagen buildup in small pulmonary arteries. Additionally, smaller arterioles become more muscular, and venules develop abnormal thickening of their inner lining (intimal proliferation). This damage is worsened by progressive fibrosis in lung tissue, which destroys and obstructs blood vessels. In some cases, thrombosis can form within the pulmonary arteries further worsening the condition. Additionally, increased levels of signaling molecules like endothelin-1, fibroblast growth factor beta, and platelet-derived growth factor contribute to abnormal blood vessel remodeling, ultimately leading to pulmonary hypertension (Agrawal et al., 2016).

Diagnosing PH in clinical settings is challenging due to overlap between symptoms of PH and IPF, such as dyspnea on exertion, leading to low degree of suspicion for PH. Useful sign in physical exams to diagnose PH in patients with IPF are accentuated pulmonary heart sound, tricuspid regurgitation murmur and fixed splitting of S2. Patient with IPF can also have elevated jugular venous pressure seen on neck examination, peripheral edema, and hepatomegaly indicative of right heart failure in advanced case. Right heart catheterization is the gold standard for diagnosing PH. Transthoracic echocardiogram (TTE) can be used as less invasive method of diagnosing PH with modeset accuracy. It has 83% sensitivity and 72% specificity with correlation coefficient of 0.7 (Janda et al., 2011). Computed tomography (CT) scan of thorax may shows dilatation of right ventricle, increased diameter of main pulmonary artery >29mm, and greater diameter of pulmonary artery compared to aorta (Agrawal et al., 2016). Electrocardiogram may shows P-pulmonale and qR in V1 but the sensitivity and specificity are low (Seyyedi et al., 2019).

Treatment options for PH-IPF is limited. Studies testing endothelin receptor antagonists, such as ambrisentan, and phosphodiesterase 5 inhibitors, such as sildenafil, to treat PH linked to ILD showed no benefit. There's limited reliable data on PH-ILD treatments, and some medications even seemed harmful. For example, ambrisentan increased worsening in ILD patients, and riociguat raised risks in PH-ILD patients. According to the European Society of Cardiology and European Respiratory (ESC/ERS) guidelines, currently there is no sufficient evidence to recommend the use or against the use of PDE5 inhibitors. Severe PH-IPF patient should be referred to tertiary hospital with expert in pulmonary hypertension while optimizing the treatment of IPF and chronic hypoxia (Raghu, 2013; Humbert et al., 2022; Nathan et al., 2019). The use of supplemental oxygen with decreasing diffusing capacity, as measured by DLCO (diffusing capacity for carbon monoxide), have been shown to significantly increase the survival of patient.(Farber et al., 2018) Long term oxygen therapy is used with low flow oxygen device (e.g. nasal canule) with targeted PaO2 high enough to prevent hypoxemia and low enough to prevent carbon dioxide (CO2) retention. This usually achieved in oxygen saturation (SaO2) of 94-98%. If patient is suspected or have history of CO2 retention, SaO2 target should be lowered to 88-92% (O'Driscoll et al., 2017).

Promising results came from Increase trial studying inhaled treprostinil for treatment of PH-ILD. Unlike other medications, inhaled treprostinil shows promise for treating PH-ILD. This study tested inhaled treprostinil on 326 patients with confirmed PH-ILD. Patients inhaled 72 ug of treprostinil four times a day for 16 weeks. Compared to a placebo, inhaled treprostinil significantly improved patients' walking distance (6-minute walk test) by 31 meters. It also led to lower levels of a marker for heart strain (NT-proBNP) and fewer instances of

patients getting worse, mainly because fewer patients experienced a large decline in walking distance. The use of treprostinil may be considered for patient with PH-IPF, however the long term benefits of treprostinil on PH-IPF is still unclear (Waxman et al., 2021).

Idiopathic Pulmonary Fibrosis and arrythmia

The most common arrythmia seen in patient with IPF is atrial arrythmia. Among atrial arrythmia, atrial fibrillation (AF) and atrial flutter is the most common type reported. Among patient who undergo lung transplantation, IPF is a strong predictor of atrial fibrillation with odd ratio of 2.3 (Agrawal et al., 2016). Another study examining COPD and IPF patient shows that the decreases in forced expiratory volume (FEV) and forced vital capacity (FVC) during spirometry are independent risk factors for the development of AF. It is believed that IPF increase the risk of arrythmia through the presence of hypoxia, elevation of pulmonary pressures, increased risk of coronary artery disease, and the presence of chronic inflammation. Hypoxia is known to increase the sympathetic activity of the body which causes increased risk of arrythmia. Trigger for atrial fibrillation can also be found around pulmonary veins, especially in atrial muscle sleeve. Atrial muscle sleeve of the pulmonary veins is a layer of cardiac muscle that extends from the posterior wall of the left atrium onto the pulmonary veins (Gupta, Kaur & Sahni, 2022). Study found that pacemaker-like cells can be found around pulmonary veins creating burst of ectopic beats (Mahida et al., 2015). Therefore, any disturbance in pulmonary pressure may trigger AF. Arrythmia in patient with IPF can also be caused by the coronary artery disease (Agrawal et al., 2016).

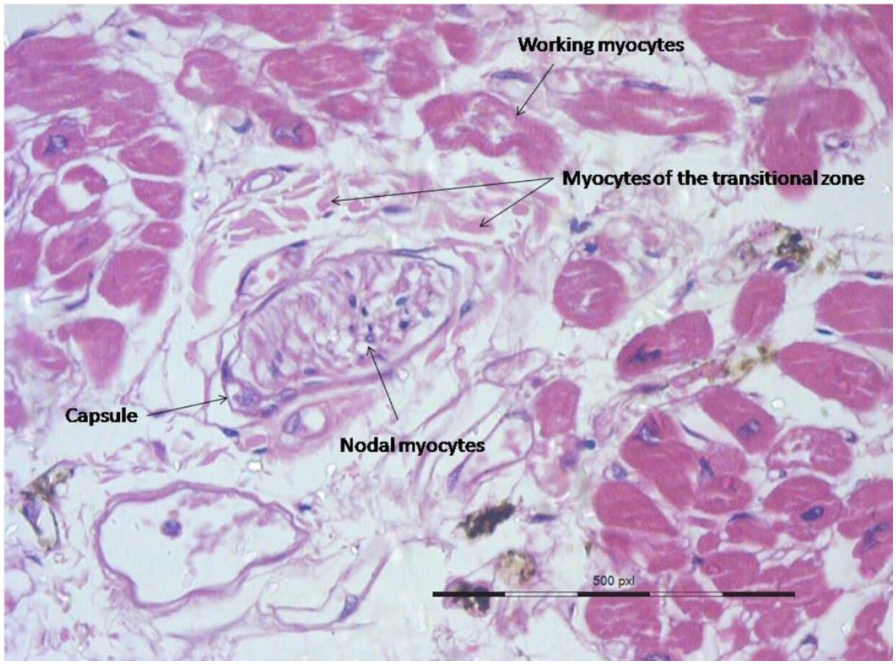

Figure 6. Node-like structure found within the cardiac muscle bundles of the atrial muscle sleeve (Gupta, Kaur & Sahni, 2022).

The treatment of arrythmia in IPF patient is similar to patient without IPF. According to the 2020 ESC guidelines, atrial arrythmia should be treated with ABC approach, namely A for Anticoagulant/Avoid Stroke, B for Better symptom management, and C for Cardiovascular and Comorbidity optimization. Warfarin is widely used as anticoagulant and stroke prevention. Common dose used is 2-5 mg per day with INR target of 2.5 (range 2 to 3)

(Anderson et al., 2023). Other vitamin K antagonist that commonly used are apixaban (2x2.5 mg – 2x5 mg), dabigatran (2x150mg), edoxaban (1x60mg), and rivaroxaban (1x20mg) (Beck & William M. King, 2014; January et al., 2014). Aspirin and clopidogrel are less effective for prevention of stroke, systemic embolism, myocardial infarction, and vascular-related mortality (Hindricks et al., 2021).

Better symptom control can be achieved by administering rate controller. The initial heart rate target is <110 bpm. If the symptoms persist, stricter heart rate target of <80 bpm may be used. The pharmacological therapy that are commonly used as rate controller are beta-blockers, digoxin (loading dose 10-15 mcg/kg and maintenance dose 0.125-0.5 mg/day), diltiazem (120-240 mg/day), verapamil (240-320 mg/day), or combination therapy. Anti arrythmic drugs also have rate-limiting properties, however amiodarone in particular should be avoided in IPF patients. Amiodarone have adverse effect of inducing pulmonary fibrosis. In patient consuming regular amiodaron, especially in higher dose of >400mg/day, phospholipid complexes may accumulate in histocytes and type II pneumocytes.This complexes induce inflammation and manifest in various radiological changes ranging from lung nodules, organizing pneumonia,chronic interstitial pneumonia, pulmonary fibrosis, to diffuse alveolar damage. Therefore, in patient with IPF amiodarone should be avoided since the existing radiological changes in IPF (honeycombing and traction bronchiectasis) might mask the pathological changes in radiology caused by amiodarone (Budin et al., 2022; Hindricks et al., 2021).

The C component of ABC management include controlling the cardiovascular risk factors and comorbidities. Body mass index should be optimized since obesity increase the risk of AF, ischemic stroke, and thromboembolism. Alcohol use and smoking should be cessated. Caffeine consumption does not directly increase risk of AF, however the palpitation related to caffeine consumption may be associated by patient as symptoms of AF. Other comorbidites such as hypertension, diabetes melitus, sleep apnea, and IPF that increase risk of atrial arrythmia should be treated accordingly (Hindricks et al., 2021; Vahdatpour, Luebbert & Palevsky, 2020).

Another treatment option for atrial arrythmia is cardiac ablation. Cardiac ablation is a procedure using flexible cathether inserted into blood vessel to treat arrhythmias by selectively destroying specific areas of the heart tissue that are causing the abnormal electrical signals. There is no absolute contraindications in performing cardiac ablation in patient with IPF. According to study conducted by Roh, et al, cardiac ablation can be safely performed in patient with chronic lung disease with comparable outcome (Roh et al., 2011). However, when considering cardiac ablation for atrial arrhythmias in patients with IPF, clinicians have to weight the risk and benefits especially in patient with severe IPF. Patient with severe IPF have lower tolerance to invasive procedure. Acute exacerbation of IPF and postoperative pneumonia have been identified as important postsurgical complications in both thoracic and nonthoracic surgical populations (Carr et al., 2022).

Idiopathic Pulmonary Fibrosis and Coronary Artery Disease

Studies have shown association between IPF and coronary artery disease (CAD). Study by Kizer et al shows that patient with pulmonary fibrosis have increased risk of having CAD compared to patients with non fibrotic lung disease (OR 2.18; 95% CI, 1.17 to 4.06) (Kizer et al., 2004). It is believed that the main pathway IPF causes CAD is through the chronic inflammation. Patient with IPF have increased serum levels of cytokines, interleukins, and circulating immune complexes. Tumor necrosis factor-α (TNF-α), interleukin-4 (IL-4), and interleukin-8 (IL-8) play role in angiogenesis. In particular IL-4 and TNF-α have role in upregulating cell adhesion

molecules that causes accumulation of leucocyte in vascular intima. The IL-13 along with IL-4 also upregulate lipoxygenases that results in accumulation of low-density lipoprotein (LDL) in vascular intima (Sinha et al., 2024). Patient with IPF also shows development of fibrosis in extra-pulmonary organs like the mediastinum and fingers. In clubbing fingers, commonly found in IPF, involves fibroplasia and neovascularization. Since fibroproliferative processes can be found outside the lungs, as evidenced by clubbing finger and the systemic presence of related mediators, IPF may be able to also cause fibrotic and atherogenesis process in coronary artery. In patients with concomitant disease of CAD-IPF, IPF may also worsen the CAD by exposing body to chronic hypoxia. Systemis hypoxia may worsen the symptoms of angina. Patient with IPF-CAD also tend to prioritize the IPF medication and less attention to the CAD. Study shows that patients with IPF-CAD less likely to to receive routine statins and beta-blocker compared to general population (Agrawal et al., 2016; Hubbard et al., 2008).

There are several pharmacological and nonpharmacological treatments for coronary artery disease. Nonpharmacological treatments mainly include the changes in lifestyle such as qutting smoking, normalizing the body mass index, and changing daily diets. Sometimes invasive treatments such as stent placement and coronary artery bypass graft (CABG) is needed to fix the blocked artery. Pharmacological treatments may include the use of anticoagulant, betablockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers, and statins. Currently no contraindication exist that hinder the pharmacological treatment of CAD in patients with IPF. Aspirin 80-160 mg per day may be used to prevent the worsening of CAD and may provide benefit for IPF. Evidence suggest that aspirin can ameliorates pulmonary fibrosis through a PI3K/AKT/mTOR-dependent autophagy pathway (Peng et al., 2023). Furthermore, metaanalysis published by Zhang, et al in 2021 shows that the regular use of statins improve the outcomes of patients with CAD-IPF even after adjusting the confounding factors. The CAD-IPF patients who receive statins as routine treatment experience reduction in mortality with hazard ratio of 0.89 (95% CI 0.83–0.97). The choice of statins used is simvastatin 20mg/day, atorvastatin 20mg/day, or rosuvastatin 10mg/day. The use of ACEi or ARB also shows trend in mortality reduction but not statistically significant (HR, 0.92; 95% CI 0.73–1.15). Therefore, it is important to emphasize the importance of statins in patient with CAD-IPF (Zhang et al., 2021).

Idiopathic Pulmonary Fibrosis treatment and its effects on heart

Currently no curative treatment available for IPF. The two most promising drug available work to slow the progression of IPF are pirfenidone and nintedanib. Pirfenidone works by reducing fibroblast proliferation, inhibit transforming growth factor, inhibit collagen production, and reduce the production of fibrogenic mediator. The ASCEND trial investigated Pirfenidone in 555 IPF patients through a phase 3 randomized controlled trial (RCT). When contrasted with a placebo, Pirfenidone demonstrated a decrease in disease progression, evidenced by improvements in lung function, exercise tolerance, and progression-free survival among individuals with idiopathic pulmonary fibrosis. The predominant side effects associated with Pirfenidone were gastrointestinal, with no reports of cardiac side effects. These findings were consistent with those of the CAPACITY trial, conducted across 113 centers in 13 countries (Agrawal et al., 2016).

Nintedanib operates as a multiple-tyrosine kinase inhibitor, targeting multiple receptors involved in the process of fibrosis. The primary mechanism of action involves inhibiting the activity of certain receptor tyrosine kinases (RTKs) that are implicated in fibrotic signaling pathways. Specifically, nintedanib inhibits the activity of three

key receptors: vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR). Nintedanib can also inhibit the activity of TGF-β. The blocking of these receptors interferes with the signaling cascades that promote fibrosis. It inhibits the activation and proliferation of fibroblasts, which are cells responsible for producing excess collagen and other extracellular matrix proteins characteristic of fibrotic tissue. Additionally, nintedanib may suppress the formation of new blood vessels (angiogenesis) within fibrotic lesions, further impeding the progression of fibrosis (Rangarajan et al., 2016).

Studies done by Richeldi, et al to examine the safety of nintedanib in pulmonary fibrosis. In this study, the most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups. Cardiac events occurred in 9.7% of patients in intervention group and 9.3 percent in placebo group. No statistic test were done in the study but not likely to be significant (Richeldi et al., 2014).

Prevention of Heart Disease in IPF patient

Currently there is no specific guidelines regarding the prevention of cardiovascular complications of IPF. Patient should optimize the available treatment to slow down the progression of IPF and prevent the complication of IPF. Pulmonary function tests every 3 to 6 months is useful to monitor the progression of IPF. Serial chest imaging using HRCT is useful if patient clinically worsen and should be performed based on symptoms and the disease's progression. The 6-minute walking test is useful to assess the patient's functional status.

Antifibrotic medications approved for treating IPF include pirfenidone and nintedanib, which belong to the class of tyrosine kinase inhibitors. Clinical evidence indicates that while both drugs can decelerate the progression of the disease, their impact on mortality rates is not significant. Consequently, it is advisable to commence treatment early. Additionally, research suggests a reduction in IPF exacerbations with the use of these medications. However, its use may be restricted according to the insurance coverage. Currently both drugs are not covered in Jaminan Kesehatan Nasional of Indonesia (JKN) (Krishna, Chapman & Ullah, 2024).

Other supportive measures suggested are quitting tobacco, providing oxygen therapy, and managing gastroesophageal reflux using proton pump inhibitors. Vaccination against influenza and pneumococcus is advised to prevent secondary infection. While corticosteroids, immunosuppressants like azathioprine, and N-acetyl cysteine were previously utilized, recent recommendations advise against their use in IPF due to findings from the PANTHER-IPF trial (The Idiopathic Pulmonary Fibrosis Clinical Research Network, 2012). Mycophenolic acid is an inexpensive alternative for treatment of IPF. Patient receiving mycophenolic acid shows trend toward reduction in FVC decline, but evidence shows varying result with some show significant improvement while other shows no improvement. It is used in IPF mainly as steroid-sparing immunosuppressant (Brown et al., 2021).

In patients with chronic hypoxia, long term oxygen therapy (LTOT) is very important as chronic hypoxia leads to various cardiovascular complications. The LTOT is considered as inevitable treatment for any IPF patient. It is advisable to encourage patients to prepare for ambulatory LTOT facilities early after the diagnosis. Early referral for lung transplantation is recommended, particularly for patients experiencing a progressive decline in lung function. Research indicates a survival advantage for IPF patients undergoing lung transplantation. However, its availability is very dependent on the capability of the local healthcare capacity (Krishna, Chapman & Ullah, 2024). The need for LTOT depend on arterial oxygen tension (PaO2) and pulse oxygen saturation (SpO2). In most patients, PaO2 < 56 mmHg or SpO2 < 89 mmHg indicates the

need for LTOT. Some patients with concomitant disease, such as cor pulmonale or heart failure, need LTOT when PaO2 < 60 mmHg or SpO2 < 90 mmHg. The LTOT may also be indicated during sleep if PaO2 falls >10mmHg or SpO2 >5mmHg during sleeps with clinical symptoms of hypoxemia including morning headache, insomnia, and impaired cognitive function. In earlier stage, oxygen therapy may also be administered only during exercise or moderate-intensity activity (Abuserewa, Duff & Becker, 2021). Blood gas analysis is important to be taken prior to administering LTOT. Oxygen therapy fraction and flow should be accurately calculated to determine the optimal dose to correct hypoxemia while minimizing the risk of CO2 retention. In general, a PaO2 of 60-65 mmHg or SpO2 of 90%-92% is generally considered an adequate range. This range also gives the least risk for oxidative stress caused by the oxygen therapy (Abuserewa, Duff & Becker, 2021).

CONCLUSION

Idiopathic pulmonary fibrosis (IPF) is a chronic, fibrosing interstitial pneumonia that have various complications including cardiovascular complications. It is a diagnosis of exclusion and can be diagnosed after considering the clinical, laboratory, and radiological examination. Common cardiac complications of IPF is pulmonary hypertension, arrythmia, and coronary artery disease.Treatment for pulmonary hypetension, arrythmia and coronary artery disease is similar for patients with IPF comorbid compared to patient without it. Pulmonary hypertension develops in IPF through various pathway with hypoxia inducible factors as central component. Arrythmia can be triggered by IPF through disturbance in pulmonary veins pressure. Coronary artery disease is associated with chronic inflammation exist in patients with IPF. Currently no specific guidelines available regarding the optimal prevention for cardiac complications in patients with IPF. No curative treatment available for IPF, existing treatment can slow down the progression of IPF. This paper shows that more research is needed to improve the management of cardiac complications in IPF.

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