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# Renin-angiotensin system and idiopathic pulmonary fibrosis: What is the link?

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**ABSTRACT**
Interstitial lung diseases comprise a heterogeneous group of non-neoplastic diseases with varying degrees of inflammation and/or fibrosis. Some with known causes, others with varied etiologies that are not always identified, the so-called idiopathic interstitial pneumonias. Among them, idiopathic pulmonary fibrosis (IPF), considered a prototypical fibrotic disease1,2. IPF is a non-neoplastic progressive lung disease with different degrees of inflammation and fibrosis, the clinical manifestation of which is progressive dyspnea. The etiology and pathophysiological mechanism of the disease are quite complex and not fully understood, hindering effective therapeutic alternatives. Evidence in the literature demonstrates the involvement of Angiotensin II (Ang II), the most studied vasoactive peptide of the renin-angiotensin system involved in the pathogenesis of fibrosis. In this context, it is possible to believe that the imbalance of the Renin-Angiotensin System (RAS) in favor of the fibrosing axis (Ang II/AT1) is associated with the development of pulmonary fibrosis (PF) and functional impairment of patients. On the other hand, the counter-regulatory and protective axis of the RAS, the peptides Angiotensin 1-7 and Alamandin, may be an alternative treatment of PF. Therefore, new interpretations of the participation of this system in the pathophysiology of IPF may contribute to elucidate the mechanisms involved in this disease, which still has no cure, which is highly costly for the health system and especially for the development of therapies that improve the quality of life of these patients.

**Keywords:** Idiopathic pulmonary fibrosis, Renin-angiotensin system, Therapeutics, Lung transplantation.

## 1 INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common interstitial lung disease3. It occurs slowly and irreversibly, with a high mortality rate. Possibly, the lack of uniformity at the time of care still hinders its diagnosis4. Currently, the most accepted hypothesis for the pathogenesis of the disease is fibroproliferation and excessive accumulation of extracellular matrix. This event in the lung tissue occurs during the repair of alveolar epithelial lesions with the release of pro-inflammatory mediators5.

Thus, IPF may be associated with aging and a progressive fibrosing condition of the lungs, also related to smoking6. Males represent the most affected population, usually in the sixth or seventh

decades of life7. Loss of lung elasticity and thickening of alveolar membranes leads to limited respiratory capacity. The effort of the accessory ventilatory muscles to compensate for the loss of pulmonary gas exchange function occurs at the expense of high energy expenditure, which, added to the difficulty in eating caused by dyspnea itself, leads patients to weight and muscle mass loss, as well as quality of life8.

Among the possible causes of IPF, some evidence emerges to try to explain the pathophysiology of the disease. In this context, the renin-angiotensin system (RAS) may play a key role in modulating the fibrotic process. The peptides of this system have receptors in several target organs, such as the heart, blood vessels, and especially in the lungs, and may be membrane-bound or soluble in plasma9.

Due to the insidious nature of the disease and the lack of specific clinical signs, diagnosis of IPF is often delayed. This delays the start of treatment and compromises the effectiveness of therapeutic interventions. The identification of biomarkers to indicate the presence of the disease in earlier stages would be of great value for the success of the treatment, enabling a more accurate diagnosis and the early initiation of therapy.

## 2 OBJECTIVE

To review the literature on the role of the renin-angiotensin system in the pathogenesis, progression, and potential therapeutic strategies for IPF.

## 3 METHODOLOGY

This is a literature review based on articles published in the following databases: PubMed, LILACS, SciELO and MEDLINE. The survey took place in August and September 2023.

## 4 LITERATURE REVIEW

### 4.1 CONCEPT AND EPIDEMIOLOGY

IPF is a chronic non-infectious, progressive disease restricted to the lungs, without a defined cause, in which healthy lung tissue is eventually replaced by scar tissue. This tissue replacement impairs pulmonary function and, consequently, gas exchange10.

Interstitial lung disease has the worst prognosis and early mortality11,12. In addition, it mainly affects men over 60 years of age and, after diagnosis, the average survival is only 3 years11.

Despite being a rare disease, the mortality of affected patients has been increasing worldwide in the twenty-first century, reaching between four and ten deaths/100,000 inhabitants in several countries in Europe, North America, Asia and Oceania13. In recent years, this reported increase in prevalence and incidence14, associated with the high mortality rate, has drawn attention to the need

for new therapeutic alternatives that enable an effective improvement in the quality of life and longevity of patients.

In Brazil, few epidemiological data are available on IPF. One of the possible reasons is due to the difficulty of diagnosis, which often occurs due to exclusion, and the small number of centers specialized in this disease. In this sense, the temporal analysis of mortality in Brazil shows, between 1979 and 2014, that mortality coefficients are lower than in other countries, which may indicate underreporting15. Even so, the country follows the global trend in terms of gender and age of people affected by the disease15.

## 4.2 PATHOPHYSIOLOGY

In the pathophysiology of fibrosis, microlesions are present that cause inflammatory reactions, followed by a disordered healing response. This process is characterized by different degrees of fibroblast activation, collagen accumulation that causes thickening of the interstitium and pulmonary stiffness16. As a consequence, there is thickening of the alveolar walls and distortion of the pulmonary architecture17. Histologically, it has an irregular appearance, with preserved areas, areas of fibrosis, and honeycomb-like formations that alternate in the parenchyma. Usually, the subpleural and paraseptal regions and the pulmonary bases are the most affected18.

In addition to non-functional repair, due to the progressive increase in collagen deposition, the presence of short telomeres is observed, associated with protein and mitochondrial dysregulation and oxidative stress19. Together, this process causes accelerated aging. These, among other factors, occur from the beginning and during the evolution of fibrosis also mediated by pro-inflammatory interleukins and by transforming growth factor beta (TGF-β), produced by the cell in different ways20.

New studies have shown that TGF-β1, expressed by macrophages, is directly involved in the progression of IPF and, therefore, seems to be an important target for the formulation of a new therapy21. As the repair mechanism advances, the release of cytokines and growth factors intensifies the deposition of interstitial tissue, demonstrating the importance of the molecules present in the tissue for the development of IPF.

The initial events of IPF, characterized by fibroblast activation, are not yet fully understood, but the most accepted hypothesis is the exposure of genetically susceptible individuals to risk factors such as smoking11. These alterations that affect patients with IPF compromise the functional capacity of the lungs and have repercussions on the worsening of quality of life17.

In this inflammatory scenario, the RAS has been growing in importance. In addition to the well-known actions on hydroelectrolyte balance and blood pressure, this system has been related to fibrotic processes in several systems.

Classically, the activation of the RAS initiates by the action of the enzyme renin, produced by the juxta-glomerular cells located in the renal afferent arteriole. Once in the bloodstream, renin converts angiotensinogen into angiotensin I (Ang I), a decapeptide that has little vasoconstrictor22. By the action of angiotensin-converting enzyme (ACE), Ang I is converted into the angiotensin II (Ang II) octapeptide, which has several physiological effects. Among them, Ang II activates the enzyme NADPH oxidase in vessels and tissues and causes oxidative stress23.

The effects of Ang II are mediated by two G-protein-coupled membrane receptors, called AT1 and AT223 receptors. The AT1 receptor is involved in the classical effects of Ang II and when exaggeratedly activated, can induce deleterious effects on tissues such as inflammation, oxidative stress and fibrosis. Activation of this receptor induces fibrosis, vasoconstriction, fluid retention, and apoptosis24,25. The actions of Ang II on the AT2 receptor, in turn, are commonly opposite to those on the AT1 receptor, and the affinity of Ang II for this receptor is much lower26.

In the lungs, Ang II stimulates fibroblasts to synthesize extracellular matrix. Type I collagen is the main matrix protein in the pulmonary interstitium. When in excess, this collagen, synthesized by activated fibroblasts, participates in the fibrotic process. Among other actions, it causes thickening of the alveolar walls and reduction of pulmonary compliance. These alterations affect the respiratory capacity of patients and make it difficult to obtain oxygen for tissue perfusion11.

In recent years, studies on the RAS have shown the existence of several peptides that make the system much more complex. Among the peptides and receptors discovered, we can mention the angiotensin-converting enzyme 2 (ACE2), which cleaves Ang I to form angiotensin 1-7 (Ang-1-7). Ang 1-7 binds to the Mas receptor and triggers vasodilator, antiproliferative, antifibrotic and anti-inflammatory effects27. For these reasons, Ang 1-7 has the ability to protect the lungs and acts as an antagonist peptide to the effects of the axis represented by Ang II.

Similarly, in 2013 two other components of the non-classical axis were discovered, Alamandine (ALA) and the MrgD28 receptor. ALA is a heptapeptide analogous to Ang 1-7, differing structurally by the substitution of the amino acid aspartate by alanine at position 1. It can also be formed by the action of ACE2 on Ang A, or by the decarboxylation of Ang 1-729.

ALA acts through the G protein-coupled membrane receptor, called MrgD30. This new axis, ACE2-ALA-MrgD, appears to be potent in counterregulating the effects of the ACE-Ang II-AT1 axis. ALA has an antioxidant, anti-inflammatory, and antifibrotic effect, with actions similar to Ang-1-731. In view of this, both the ECA2-Ang-(1-7)-Mas axis and the ECA2-ALA-MrgD are promises in promoting effects that oppose the deleterious effects of the exaggerated participation of Ang II.

In fact, IPF can be considered a multifactorial disease in which environmental stimuli activate endogenous factors and result in a disordered cellular repair process. Once the fibrotic process has

begun, there is no way to reverse it, and the disease may have a gradual or rapid course. Unfortunately, the decline in organ function is inevitable and often leads to death17.

## 4.3 SIGNS, SYMPTOMS, AND COMPLICATIONS

The etiology of IPF is associated with an abnormal repair process after an injury to the lungs. The accumulation of collagenous scar tissue causes thickening of the interstitium and pulmonary stiffness11,16 and affects the respiratory capacity of patients. Thus, it hinders the obtaining of oxygen for tissue perfusion, representing a major therapeutic challenge for pulmonologists.

The first clinical signs of interstitial lung diseases are nonspecific. The patient presents cough, dyspnea, fatigue and weight loss, impairing the early diagnosis. Of these, dyspnea is the most common and initially manifests itself in association with physical exertion. However, as the disease progresses, this dyspnea can occur even at rest. Pulmonary auscultation shows teleexpiratory crackles during expiration, which predominate in the lower middle third of the thorax8.

As the disease progresses, patients may also present tachypnea, tachycardia, hypoxemia, and enlargement of the distal phalanges of the fingers and fingernails, also known as digital clubbing16,32. Usually, by the time symptoms are noticeable, lung damage is already at an advanced stage, requiring immediate medical follow-up.

Among the possible complications, the presence of secondary pulmonary hypertension occurs in the most advanced cases of pulmonary fibrosis, which places about 60% of patients under evaluation for transplantation8. In addition, pulmonary embolism, infections, acute lung injury, and neoplasms are possible complications, which, when present, lead to a mortality rate close to 100%[33] in a short period of time.

## 4.4 TREATMENT

With the increasing evolution in the understanding of the pathways involved in the development of IPF, this is the only interstitial lung disease with established therapy16. The combination of N-acetylcysteine, azathioprine, and prednisone was one of the first attempts at treatment for IPF. However, there was not much success, worsening the prognosis and increasing the risk of mortality due to recurrent hospitalizations34.

Other immunosuppressants have also been tested, such as cyclophosphamide and mycophenolate, which have also shown no clinical benefits in patients with IPF. As for the use of Thalidomide, a drug with anti-inflammatory properties that can cause congenital malformation, there is a need for strict sanitary control. It was tested in an experimental model, but was not administered to patients with IPF35 due to the risks it represents.

Currently, the recommended therapy for the treatment of IPF involves attempting to decrease the fibrotic process. Nintedanib or pirfenidone, supportive therapies, do not stop progression or reverse existing fibrosis. Although both drugs are effective in slowing the progression of the disease37 and reducing the decline in lung function, they do not modify the mortality rate and have debilitating side effects, such as vomiting and diarrhea17,38.

On the other hand, although they are internationally recommended drugs14 for the treatment of IPF, the Unified Health System (SUS) does not provide these drugs. They are not part of the drugs approved by the National Commission for the Incorporation of Technologies in the SUS39.

Due to the chronic nature of IPF, initiating therapy early may represent therapeutic efficacy. This would avoid significant modifications in lung architecture. In addition, in this context of severity, after COVID-19 and the need to understand the SARS-CoV-2 virus, the participation of RAS in lung disease became a little clearer.

In this sense, data from the literature demonstrate that the angiotensin-converting enzyme type 2 (ACE-2) receptor represents one of the ways in which the virus enters the lung cell40. This finding highlights the strong impact of RAS participation in pulmonary pathophysiology.

In fact, results also demonstrate that patients with IPF have a plasma imbalance between the axes of the components of the RAS. When compared to healthy individuals, patients with IPF had similar plasma concentrations of Ang I, Ang II, Ang-(1-7). However, the plasma concentration of ALA was almost four times lower in these patients41. These results indicate that, possibly, in IPF there is an imbalance between the participation of the classical axis (ACS-AngII-AT1) and the contemporary axis (ACE2-Ang 1-7/ALA-Mas/MrgD) of the RAS. Quite possibly, ALA has a protective effect against pulmonary fibrosis.

In addition, the literature also points to a higher expression of AT1 receptors and a lower expression of the Mas receptor in the lung tissue of patients with IPF42. Taken together, these findings indicate that the protective axis, represented by ALA and Ang-(1-7), is probably less active in these patients.

Considering these findings in patients with IPF, ALA can be an alternative treatment, even if adjuvant, to what has been recommended and is currently available. Further studies, both preventive and curative, are needed to evaluate the role of endogenous regulators in the pathophysiology of IPF. The administration of an anti-inflammatory drug such as ALA may, in the future, be considered a therapeutic strategy to reduce, perhaps stop, the evolution of this limiting disease.

As the disease progresses, lung transplantation is the only option that can increase the survival of these patients43, and it is urgent to find treatment alternatives that improve the prognosis. Historically, the first lung transplant performed in Latin America was in May 1989, in the city of Porto Alegre, which is now a referral center for transplants44.

However, in Brazil, this option is still very limited. There are few referral centers for this type of transplant and few donors45. There is a difficulty in finding the necessary compatibility to perform a transplant. Thus, in Brazil, 146 adult patients are waiting on the lung transplant waiting list 46. Regardless of the proposed treatment, the association with the pulmonary rehabilitation program in symptomatic patients is essential for the physical capacity and quality of life of these patients43.

## 5 CONCLUSIONS AND PERSPECTIVES:

In recent years, with technological advances in health, numerous strategies have been studied and used to delay the progression of the disease and improve the quality of life of these patients. In this context, the RAS may represent an important therapeutic target, with the endogenous peptide alamandine as its protagonist, which opposes the effects of Ang II.

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