Impact of oxygen therapy on quality of life in patients with Idiopathic Pulmonary Fibrosis and hypoxaemia

FINAL DEGREE PROJECT

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1. Abstract

Background

Most of the patients that suffer from Idiopathic Pulmonary Fibrosis (IPF) end up experiencing hypoxaemia at some point of their pathologic progression. That is expressed in desaturation (SpO_2) of blood oxygen (O_2) in a pulse oximetry, dyspnoea and a worsening of the quality of life with it. All patients with Chronic Respiratory Insufficiency (CRI), with basal blood gasometric levels of less than SpO_2 89% or PaO_2 60 mmHg, are treated a minimum of 15 hours per day with domiciliary O_2 therapy in order to hold these levels up to an acceptable threshold. However, this prescription is based in low quality evidence and most of it is brought by analogy from the evidence reported in patients with Chronic Obstructive Pulmonary Disease (COPD)(1)(2)(3). Even today mildly hypoxic patients are treated with oxygen depending on subjective factors and no statistically significant studies have been conducted in patients with IPF to prove oxygenotherapy's positive or negative effects(4). Furthermore, since the prognostic of IPF is poor and its course is torpid, to improve the patient's quality of life, and to report what role oxygen might play in that, has to be a priority.

Objective

The main objective of this study is to evaluate the impact of continuous domiciliary oxygen therapy in patients with IPF and with chronic hypoxia but without CRI, and see if their quality of life, their physical and respiratory capacities and their survival expectancy are improved.

Design

This trial will be a prospective, multicentric, controlled and randomized study.

Methods

All subjects (N= 358) will be enrolled consecutively in various sanitary centres and assigned randomly to a group intervention (n_1= 179) or a group control (n_2= 179). The first ones will receive a minimum of 16 hours of continuous oxygen therapy a day for 2 years, while the second group will not. A third group (n_3=97) of patients with basal SpO2< 89% and/or basal PaO_2 <60 mmHg (CRI) will be followed with the same O_2 prescription to see their progression throughout the disease course.

We defined the primary outcome as the punctuation stated by the participants in a quality of life questionnaire called EuroQol-5D-5L (see **annex 1**). Secondary outcomes will be number of hospitalisations due to any cause, number of acute exacerbations and time to the first one, a comparison of the dyspnoea between two groups through mMRC scale, the evolution in the 6mWT and functional respiratory parameters (measured in RFT) and the survivors rate at 5 years.

Participants

Patients with a certified diagnose of IPF, under 80 years old, with a basal blood SpO_2 of <95% and RFT with FVC 50-80% and a DLco >35% will be welcome to participate.

1. Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
APTT	Activated Partial Thromboplastine Time
BAL	Bronchio-Alveolar Lavage
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRI	Chronic Respiratory Insufficiency
C-RP	C-Reactive Protein
CTD	Connective Tissue Disease
CT90	Percentage of the sleep time the patient's SpO_2 <90%
DILD	Diffuse Interstitial Lung Disease
DLco	Alveolar diffusion of carbon monoxide
FiO_2	Inhaled fraction of oxygen
FVC	Forced Vital Capacity
FRT	Functional Respiratory Tests
GGO	Ground Glass Opacity
GSR	Globular Sedimentation Rate
G/γ -GT	Gamma glutamyl transpeptidase
HCO_3^-	Bicarbonate ion
HR	Hazard Ratio
HRCT	High-Resolution Computed Tomography
IPF	Idiopathic Pulmonary Fibrosis
MDD	Multidisciplinary Discussion
mMRC (scale)	Modified Medical Research Council (scale)
NSIP	Non-Specific Interstitial Pneumonia
OSAS	Obstructive Sleep Apnea Syndrome
$PaO_2/CO_2/HCO_3^-$	Partial blood Pressure of the following molecules ($PaO_2/CO_2/HCO_3^-$)
PH	Pulmonary Hypertension
PT-INR	Prothrombine Time- International Normalised Ratio
UIP	Usual Interstitial Pneumonia
SLB	Surgical Lung Biopsy
SpO_2	Oxygen blood saturation
6mWT	6 minutes Walking Test

2. Introduction

2.1. Idiopathic Pulmonary Fibrosis

Among the pulmonary diseases, those which affect the parenchyma in a chronic way are classified as Diffuse Interstitial Lung Diseases (DILD) or Diffuse Parenchymal Lung Diseases (DPLD). They share a common pathogenic process of fibrotic pneumonia after an erratic remodelling of the interstice when exposed to a nocive either known or unknown agent that leads to a slow but progressive decrease of the respiratory capacity of the patient. Among the many pathologies that conform this heterogenous group, the most prevalent of all is Idiopathic Pulmonary Fibrosis (IPF) (5).

2.1.1. Epidemiology

It is estimated that IPF is accountable for about 50% of all DILD's and it is defined as a chronic fibrotic parenchymal pneumonia which is limited to the lung and has no known cause. It affects mainly males from 50 to 60 years old, with an incidence rate between 4,6 and 7,4/100.000 inhabitants increasing with older age, and prevalence rates of 20/100.000 in men and 13/100.000 in women. There are approximately 7.500 cases of IPF in Spain, and in spite of the progress accomplished in the last years thanks to its earlier diagnose with the use of new criteria and treatment, it is still considered to have a poor prognosis and a relentless progression to a terminal illness in 2 to 5 years. (5). Regarding the natural progression of this illness, it may rest asymptomatic for 2 or 3 years yet most of the patients show a slow decrease of their clinical and functional status that inevitably leads to a chronic respiratory insufficiency in 5 years. However, some individuals present a relatively stable course, interrupted by acute exacerbations and other morbidities with grave consequences for the patient's health. Furthermore, a third minority of patients may present a devastating accelerated form of fibrosis that lead to a terminal insufficiency in months. All in all, the estimated life expectancy of IPF patients goes from 2 to 5 years after being diagnosed.

2.1.2. Physiopathology and pathogenesis

The physiopathology of Idiopathic Pulmonary Fibrosis is not completely understood, yet the main opinion stands for a combination of a few environmental risk factors and a genetic vulnerability that could provoke an inflammation that would start an inflammatory chain reaction. It is thought that pathogenesis of pulmonary fibrosis consists of four overlapping biological mechanisms: 1) prolonged exposure to an inflammatory agent, 2) biochemical lung response, 3) immunological response, and 4) fibrotic remodelling response (6). The constant exposure to harmful microscopic particles or fibers triggers an immunological response to expel them (clearance lung mechanisms) in the alveolar surface. When such mechanisms become

overcome, the remaining particles in the alveolus are more and more numerous, they are taken up by alveolar epithelial cells and deposited into the interstitium. From there an inflammatory cascade is unchained by macrophages, who ultimately release growth factors and mesenchymal proliferation cytokines, both hallmarks in IPF. Fibroblasts and other remodelling cells are stimulated by oxygen peroxide (oxidatory stress released by the macrophages), and therefore a proliferation of these ends up spreading fibrotic tissue throughout the pulmonary parenchyma, showing a pattern called Usual Interstitial Pneumonia (UIP) both radiological in the CT scan and histological in a biopsy.

It has been proved as well that depending on the genetic susceptibility and the characteristics of the inhaled particle the oxidant and cytotoxic process may be graver or milder (for instance, freshly cut particles of silica generate more free radicals thus causing more impact than aged particles) (6). All in all, this process is key to understand the physiopathology of IPF, for the latest theories suspect (although with little evidence) it may be a misunderstanding of the term idiopathic and that individuals with IPF might just have a greater genetic vulnerability to a lower dose of particle inhalation than other interstitial pneumonias in the DILD group. Here we expose some of the factors that are considered to increase the risk of developing an IPF (6):

Genetic factors

On the one hand, the genes involved in the IPF pathogenic development are those in charge of maintaining the telomere's length (TERT, TERC mutated telomerase genes) and are more common in its familiar form. Other mutated genes in relation with IPF are the surfactant protein C and the mucin 5 B (MUC5B) genes (5). Almost 30% of patients suffering the disease present the familiar form, with family cases or history of relatives presenting lung affection.

Tobacco

One of the main related factors to almost every respiratory disease is tobacco. A pack-year average of 20 packs/year increases the odds of developing IPF supposedly as a consequence of the diminishing of the lung's clearance capacity. That failed clearance causes more particles to be retained, and more difficulty for the immune system to absorb and wash them away (6).

Environmental risk factors

A continued exposure to silica, brass (a copper and zinc alloy), steel, wood dust or agriculture and cattle industry related jobs (or living with furry feathery animals), as well as working in the construction of wood houses, industrial car cleaning, gold extracting, diamond polishing and even technical dental work are all considered risk factors. To sum up, a continuous exposure to a dust or fume inhalation is considered a risk factor to develop the disease (6).

Gastroesophageal reflux

Many studies have shown a correlation between gastroesophageal reflux and progression to IPF.

Chronic viral infections

Although the evidence presented until now is scarce, it is thought that chronic infections by virus like the Epstein-Barr virus or hepatitis increase the risk of suffering IPF(7).

Autoimmune diseases

There is a possibility that IPF may share an autoimmune origin and pathogenesis with systemic illnesses, especially with the Connective Tissue Diseases (CTD), since their affection pattern of the lungs known as Non-Specific Interstitial Pneumonia (NSIP) shares many aspects with the UIP pattern of idiopathic fibrosis. Other patterns can be found in CTD's (8).

2.1.3.Semiology and clinical features

IPF typically affects people above the 60 years of age and it is known to have a chronic progression of symptoms from mild exertion while doing challenging physical activity at the moment of diagnosis to a terminal respiratory insufficiency at rest. Most patients suffer an initial unexplained exertional dyspnoea that is commonly accompanied by a non-productive cough. Also at the clinical exploration 50% of patients present finger clubbing and the auscultation can reveal bibasilar inspiratory crackles in 90% of them (5). A few individuals could present a worsening of the exertional dyspnoea over a few weeks, debuting with an acute exacerbation of the symptoms. These individuals show a "ground-glass" opacification pattern in the High-Resolution CT scan (HRCT) at the lower lobes, proof that fibrosis was already established. The final stages of IPF lead to a terminal respiratory insufficiency, with hypoxemia at rest (and its consequent dyspnoea) and the need of artificial devices to assist the patients breathe. Any systemic sign or symptom suggests that the pulmonary affection is part of a systemic disease, most frequently a CTD, and they must be discarded before reaching a final diagnose of IPF (7). Although very rare, some patients have presented a concurrent bone marrow failure and liver disease simultaneously with the IPF.

2.1.4.Diagnosis

Since the first American Thoracic Society (ATS)/ European Respiratory Society (ERS) Consensus (2.000) in diagnostic and therapeutic criteria was released, it has been updated in 2003 and 2013 in the SEPAR Diagnostic and Therapeutic Guidelines and in 2011 and 2018 by societies from all around the world (ATS/ERS/JRS/ALAT) in the new Diagnosis of IPF Clinical Practice Guidelines. In order to diagnose IPF three main items are required:

1. All other causes of DILD must be excluded, including all systemic diseases.
2. The HRCT scan must show a UIP pattern.
3. A specific combination of histopathological patterns with HRCT scan patterns in patients to whom a biopsy has been taken.

Thorough questioning about other possible DILD causes

According to the latest Guidelines actualised diagnostic algorithm (7), when suspecting IPF by a patients signs and symptoms, the first action must be to perform a thorough investigation of other causes that could explain the DILD. Among such questions, the physician must find out the following items:

- Detailed information about the patient's medication use, especially any history of chronic drug treatment.
- Environmental exposure to potential DILD causes both at home, at the workplace or any place the patient frequents (for example, exposure to livestock, wood or metal dust, cleaning products, stone polishing or cutting, etc.).

Serological tests to aid exclude CTDs

When the patients affection is localised in its lungs showing no other symptomatology, this clinical context does not fit rheumatoid criteria for a CTD diagnosis(8), and so, to exclude any CTD or systemic disease before reaching an IPF diagnose, the latest consensus (7) recommends the performing of serological tests. It must be emphasised that these tests do not reach or exclude any diagnose for themselves, but they complement the detailed questioning and the radiology and histopathology in order to add evidence to it. On the one hand, there's a list of tests that were recommended when facing a primary DILD to routinely exclude a CTD: blood-testing CRP (C-reactive protein), erythrocyte sedimentation or erythocite sedimentation rate (ESR), antinuclear antibodies (by immunofluorescence), rheumatoid factor, myositis panel and anti-cyclic citrullinated peptide are performed as a routine to all debuting DILD's (7). If any of these tests were to be positive the patient could be remitted to a rheumatologist to further study his case. The following tests are presented in the following table (7).

Table 1. Main serological tests carried out as a routine to exclude systemic diseases

CRP[1]	ESR[2]	ANA[3]
RF[4]	Anti-CCP[5]	Myositis panel[6]

1)C-reactive protein 2)Erythrocite Sedimentation Rate 3)Antinuclear antibodies 4)Rheumatoid factor 5)Anti-cyclic citrullinated peptide 6)Includes anti-Jo1, anti-Mi2, anti-MDA5, anti-TIF-1-γ, anti-PL7/PL12

On the other hand, many other tests are agreed to be appropriate when a certain diagnostic suspicion is at stake. Among them, specific CTD, vasculitis or rheumatoid pathologies

molecules are tested according to clinical criteria in order to discard a concrete illness, but not as a routine. Examples of that are the determination of Anti-Scl-70/topoisomerase-1, anti-centromere, anti-RNA polymerase III, anti-U1RNP and anti-Th/To when there is a strong suggestion of systemic sclerosis (scleroderma); anti-SSA/Ro and anti-SSB/La (anti-Sjögren specific antibodies) when Sjögren syndrome is suspected. When there is a strong possibility of facing a vasculitis is important to ask for the anticitoplasmatic antibodies (ANCA's). The following table shows these optional tests (7).

Table 2. Optional serological tests according to clinical suspicion.

Creatinine phosphokinase[1]	Jo-1 and others[2]	Anti MDA-5[3]	Anti Mi-2	Anti TIF-1-γ[5]
Myoglobin[1]	Anti-SRP[6]	Anti-HMGCR[7]	Anti-SAE[8]	Anti-U1RNP[9]
Aldolase[1]	Anti-PM/ Scl75[10]	Anti-PM/Scl100[10]	Anti-NXP2[4]	Anti-KU

1)Muscle enzymes **2)**Antisynthetase antibodies **3)**Melanoma differentiation-associated protein 5 **4)**Nuclear matrix protein 2 **5)**Transcriptional intermediary factor 1-γ **6)**Signal recognition particle **7)**3-hidroxy-3methylgutaryl-CoA reductase **8)**Small ubiquitin-related modifier-activated enzyme **9)**U1 ribonucleoprotein **10)**Polymyositis/Scleroderma 75*100

High-Resolution Computed Tomography scan technique

Perhaps the most crucial tool used nowadays to diagnose IPF and other interstitial diseases is a high-resolution CT scan (HRCT). Its utility relies on finding features that suggest a pattern in concordance with the hallmarks of UIP (suggestive of IPF). The features that could indicate an established UIP in a HRCT image are the finding of honeycombing, traction bronchiectasis and bronchiolectasis, the presence of a ground-glass opacity or a fine reticulation.

Honeycombing (see **annex 3**) is a pattern of groups of cystic airspaces with a diameter variation from 3 to 10mm and defined by thick walls usually accompanied by a reticular pattern of traction bronchial and bronchiolectasis. It is commonly presented as many layers of subpleural cysts or as a single layer of them, thus generating confusion sometimes between honeycombing and paraseptal emphysema.

Bronchiectasis and bronchilectasis is an indicator of pulmonary fibrosis, usually found in peripherical and subpleural areas in the UIP though it could affect the main bronchi and airway when the state of fibrosis is advanced, leaving a tortuous and thickened image of the pulmonary hilum.

Ground-glass opacification (GGO) indicates an active process. It is defined as a foggy diffuse opacity found in the pulmonary parenchyma with the preservation of the bronchi and the airway (pure GGO). In the UIP it usually spreads through the lungs combined with a fine reticular pattern and it is another marker of fibrosis. When presented, a pure GGO pattern will suggest an acute active illness is striking, mainly suspecting an acute exacerbation of the IPF. If

bronchiectasis are found superimposed to a GGO it is highly suggestive of an established IPF, discarding a pure GGO that would lead the diagnosis to an acute process.

In the absence of a previous HRCT, a bilateral GGO pattern on a background of UIP is highly suggestive of an exacerbation of an IPF, and when concordant with the clinical context it can be used to diagnose the disease.

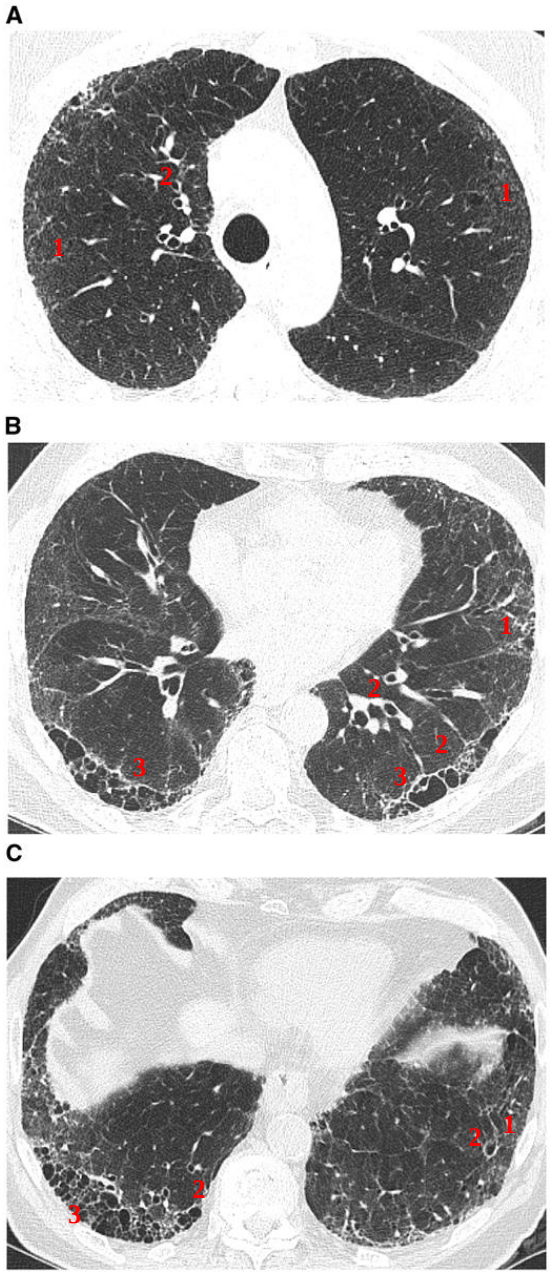
According to these features, an UIP can be established with more or less certainty. For that, the last consensus found four levels of evidence when analysing a HRCT in order to diagnose a UIP.

1. ***UIP pattern*** is the radiologic hallmark of IPF, characterised by the presence of honeycombing with or without peripheral traction bronchiectasis. It is most commonly subpleural with basal predominance, although it can be uniform throughout the lungs. That pattern can contain lymphadenopathies, GGO and ossified nodules (29%). UIP radiologic pattern seen in HRCT has a positive predictive value (PPV) of a 90-100% for a pathologic diagnose of UIP. However, a few patients that present a pathologic histopathology do not fulfil the radiologic criteria for a UIP.
2. ***Probable UIP pattern*** is a category defined by a subpleural basal distribution of reticular abnormalities including peripheral traction bronchiectasis but most importantly without honeycombing. Many patients will be considered to have an IPF when other factors are taken into consideration, such as histopathology.
3. ***Indeterminate for UIP pattern*** is considered when the HRCT shows early signs of fibrosis without honeycombing nor peripheral traction bronchiectasis. A reticular pattern or a very limited subpleural GGO can be presented without further evidence of fibrosis. About 30% of these individuals show histological patterns of UIP/IPF, so although that group does not meet criteria for a probable or UIP pattern, it is thought that an initial stage of IPF is being developed, and that must be confirmed by a prone inspiratory view in HRCT, showing that subpleural opacities are not dependent atelectasis but fibrotic areas.
4. ***Alternative diagnosis*** is a conglomerate of radiologic patterns which suggest other fibrotic DILD when HRCT is studied. These may include bronchocentric fibrosis in the upper lobes that suggests hypersensitivity pneumonitis, posterior fibrotic retraction of the hila in sarcoidosis or a vast GGO pattern sparing the subpleural space highly suspicious of nonspecific interstitial pneumonia (NSIP).

To sum up, when an HRCT study concludes that a patient has a UIP pattern and a concordant clinical condition, after having undergone a thorough questioning of environmental exposure,

no further study is required and a diagnose of IPF can be made. When the radiology shows a probable or indeterminate for UIP pattern, histological evidence is required(7).

Figure 1. Radiological UIP pattern(9).



A. Axial HRCT image of the upper lung level with mild GGO[1] pattern and peripheral mild bronchiectasis[2]

B. Axial HRCT image of the mid lung zone with abundant GGO[1] pattern, great peripheral bronchiectasis[2] and mild paraseptal reticular pattern (honeycombing combination[3])

C. Axial HRCT image of the lower lung zone with abundant septal GGO[1] pattern, multiple peripheral bronchiectasis[2] and severe subpleural reticular pattern (honeycombing combination[3])

Histopathological analysis

The analysis of lung tissue to confirm a UIP histological pattern has its utility when a HRCT image is not certain and can be obtained by different methods (probable or indeterminate UIP patterns). Nowadays the strongest recommendation supports the obtaining of a sample by surgical lung biopsy (SLB), however, in the last years transbronchial cryobiopsy is gaining strength as a diagnostic method to obtain lung tissue despite being a recent developed technique and having less experience in use, thanks to its less invasive procedure with the same results(7).

Parallel to HRCT, histopathological degrees of evidence are classified as UIP pattern, probable UIP pattern, indeterminate for UIP pattern and alternative diagnosis. They are explained below:

1. ***Histological UIP pattern*** consists of a dense fibrosis with architectural distortion (destructive scar formation and/or honeycombing) in subpleural and paraseptal lung areas, fibroblasts clusters, patchy involvements of healthy parenchyma and the absence of other features suggesting an alternative diagnosis.
2. ***Probable UIP pattern*** is suggested when one of the features mentioned before appear alone (especially if honeycombing is found alone) but to an extent that UIP is uncertain. Other features suggesting other causes of fibrosis must be absent.
3. ***Indeterminate for UIP pattern*** is formed by fibrosis with or without architectural distortion, with features favouring other UIP causes or different type of interstitial pneumonias. It combines features from a UIP pattern with characteristics of secondary causes suggesting alternative DILD diagnosis (infiltrate cellular inflammation away from the honeycombing areas in the lung, lymphoid hyperplasia or bronchiolar fibrotic distribution suggesting metaplasia).
4. ***Alternative diagnosis*** is considered when there are no fibroblasts nor signs of diffuse fibrosis, but loose clusters of it or when there is strong evidence of other diseases in the samples.

   To sum up, the following images show histological cuts of lung tissue and the changes it suffers along the IPF pathogenic process(10). After them, the following figures explain the algorithm to IPF diagnosis and the classification of evidence towards a certain diagnose according to HRCT and histopathological findings (7).

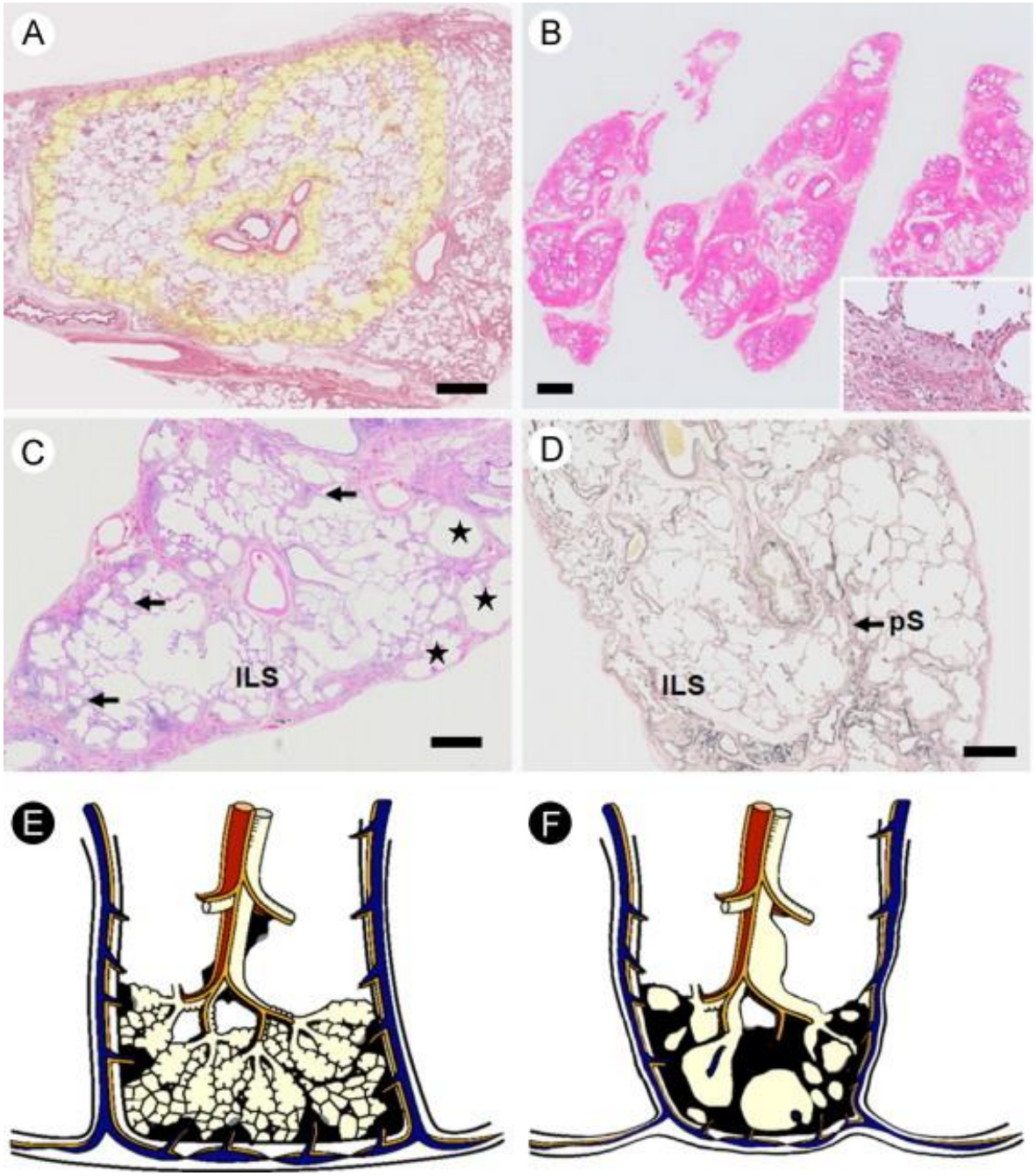
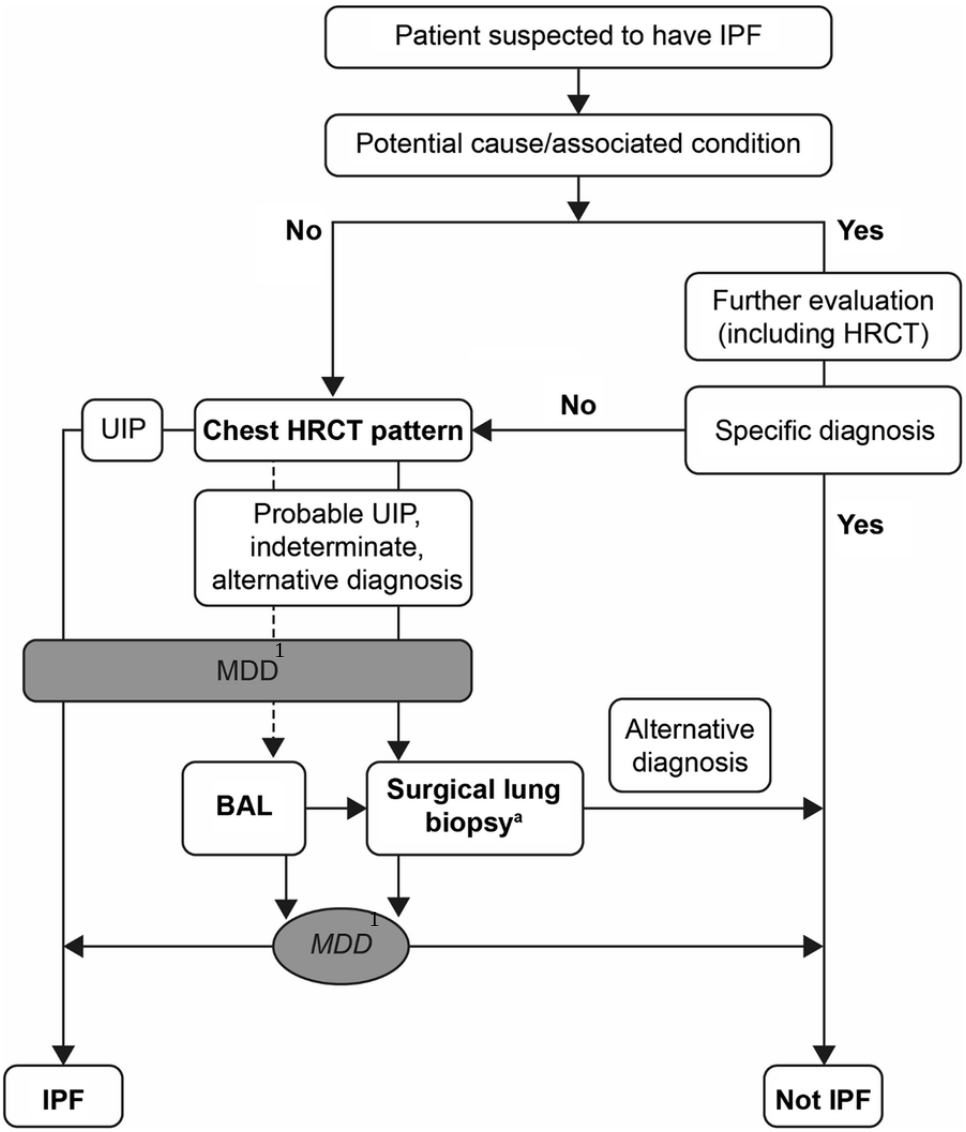


Figure 2. Histological UIP patters observed with optical mychroscope (A,B,C,D) and scheme of the pathophysiology of the fibrotic process (E,F). **A)** UIP histological pattern affecting peripheral, septal, paraseptal, subpleural and bronchovascular bundles. The areas painted in yellow are fibrotic. **B)** Low power view of UIP. Patches of fibrotic areas can be seen in dense pink. In the lower right corner is shown a fibroblast foci, indicator of temporal heterogenity and they are usually located around alveolar type II epithelium cells. **C)** Dense fibrosis in a milder distribution of UIP are indicated in perivenular areas (black arrows) and clusters of honeycombing cysts (black asterysks). The image is located in the interolobular septa. **D)** When fibrotic areas connect between them they form a septum like structure (seudoseptum: pS) dividing the lobule into smaller pieces. The differences between the seudoseptum (pS) and the interlobular septum (ILS) can be clearly stated. Scale bars are 1 mm in images A,C,D and 2 mm in B. **E)** Pathologic schema shows perivenular and peripheral fibrosis of the secondary lobule in an early phase. Adjacent normal lung tissue is present with mild destruction. **F)** Late phase of UIP or IPF with severe structural remodelling with normal lung tissue shrinkage, honeycombing cysts and traction bronchiectasis. Red lines: arteries. Blue lines: venules. Yellow lines: lymphatics. Grey lines: fibrotic foci(10).

Figure 3. Diagnostic algorithm for IPF.



1.MDD = Multidisciplinary discussion a.Other ways to obtain pulmonary samples can be considered (cryobiopsy)

Table 3. Diagnosis of IPF according to UIP patterns presented in the HRCT and histology.

IPF suspected*		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)**	Non-IPF dx
	Indeterminate for UIP	IPF	IPF (Likely)**	Indeterminate for IPF***	Non-IPF dx
	Alternative diagnosis	IPF (Likely)** /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

2.1.5.Follow up of the IPF patient

When diagnosed, all individuals undergo a respiratory and dyspnoea evaluation through questionnaires (modified Medical Research Council (mMRC) scale or Borg scale of dyspnoea) and complete functional respiratory tests which include a spirometry, pulmonary volumes and the lung capacity to transfer carbon monoxide (DLco), as well as an arterial gasometry, the 6 minutes walking test (6mWT) and an echocardiography to evaluate the hearts degree of affection.

In the mild cases of respiratory functional decreased parameters, the follow up consists of a forced vital capacity (FVC) and DLco tests, pulsioximetry at rest, 6mWT and a chest X-ray or an HRCT (depending on clinical criteria) every 3-6 months. If there is evidence of progression, an arterial gasometry, a chest HRCT and a 6mWT will be required every 3 months, to evaluate the patient's oxygen saturation and whether oxygenotherapy is needed. A HRCT could be useful if the worsening of the clinical context is important. (5)

2.1.6.Prognostic factors

There are some predictors of future morbidities and complications or survival expectancy in IPF. The factors associated with an ill course of the disease are exposed in the following table.

Table 4.	AT DIAGNOSIS	FOLLOW UP
AGE	Age > 70	
MORBIDITIES	PH[1], Cor Pulmonale, emphysema, bronchogenic carcinoma, polycythaemia	
DYSPNOEA	A low punctuation in mMRC dyspnoea scale worsening with time	A mMRC dyspnoea scale worsening with time
RESPIRATORY PARAMETERS	DLco < 40% Desaturation in the 6mWT SpO_2 < 88% or short walking distance	DLco with > 15% decrease and FVC with > 10%* decrease in 6-12 months A reduction of > 50m** in distance in the 6mWT in 24 weeks
HRCT	Extended honeycombing through the lung seen by HRCT	Spreading of honeycombing throughout the lung by HRCT in months

1)Pulmonary hypertension *Considered the main prognostic factor. If FVC diminishes > 10% in 24 weeks patients have five times more risk of death in the following year (HR=4.78) **If 6mWT distance is reduced in 50 m in 24 weeks the risk of death along that year increases four times (HR=4.27) (5)

2.1.7.Pharmaceutical treatment

Despite the latest attempts at finding a pharmacological therapy to cure IPF, none has proved effective to that end, and the treatment of the disease is basically aimed at relenting its progression, maintaining the patient's quality of life and clinical stability and preventing the

morbidities that could end the patient's life. Therefore, the drugs used since de 2015 guidelines update in the IPF treatment are the following ones:

Pirfenidone

A low molecular weight compound with anti-inflammatory and antifibrotic effects, thanks to its capacity to inhibit the fibroblast proliferation and collagen biosynthesis by transforming growth factor beta. It has also been found to inhibit tumoral necrosis factor alfa. The greatest effect Pirfenidone has is to maintain or even improve the FVC, as seen in some articles in Japan and the USA (11). Its main adverse effects are gastrointestinal (nausea, vomits, dyspepsia and anorexia), skin-related (rash and hypersensitivity) and neurological (headache and dizziness). It can increase the hepatic enzymes levels. These are usually mild or moderate reactions (11)

Nintedanib

It is a triple inhibitor of the angiokinase which blocks the receptors of the vascular endothelial growth factor (VEGF-1-3), the platelet derived growth factor receptors (PDGFR-α-β) and the fibroblast growth factor receptors (FGFR-1-3) through a competitive union to the triphosphate adenosine (ATP) binding site thus inhibiting the intracellular signalling of these receptors. This way, endothelial and perivascular cells are prevented from an erratic multiplication and new fibrosis is diminished or relented. Its main use is to prevent the decline of respiratory functionality and acute exacerbations of the disease. The most reported secondary effect is diarrhea and it can increase the hepatic enzymes levels. (11)

Although until 2015 the combination of corticoids and immunosuppressors (prednisone and azathioprine) together with N-acetylcysteine (a glutathione precursor) was currently used to treat IPF, it is no longer a therapeutic option. New evidence found that the death and hospitalisation rates as well as a liver cells damage in such combination were higher than in the placebo group (11).

2.1.8.Other therapeutic measures

Lung transplant

Because of the poor prognosis and relative effectiveness of the drugs available to treat IPF lung transplant is often considered in individuals with a moderate or severe condition. The International Society for Heart and Lung Transplant released in 2006 the criteria to be considered a suitable candidate for transplant. They are explained next: predicted DLco < 39%, a decrease in the FVC > 10% in the past 6 months of follow up, oxygen saturation <88% during the 6mWT and/or advanced honeycombing in the HRCT scan. Patients older than 65 years old

may be a relative contraindication to transplant. The survival rate after lung transplant in 5 years is estimated in 50%.

Pulmonary rehabilitation

Individuals with IPF can benefit from a routine of exercises to strengthen their lungs through aerobic conditioning, flexibility training, educational lectures, nutritional advice and psychosocial support. This has a great impact on the patient's quality of life, allowing a major autonomy in the daily life activities. It is most effective in patients with a worse baseline functional status.

Long-term oxygen therapy

It is very common among patients with IPF for oxygen (O_2) saturation in blood during physical activities to decrease drastically, thus causing an important limitation on daily life activities, exertional actions and consequently a worsening of the patient's independence and quality of life. In more advanced stages of the disease this hypoxaemia can be detected at rest. Therefore, long term oxygen aims to restore normal or acceptable blood oxygen saturation levels to improve the patient's functionality and quality of life.

2.2. Oxygen therapy

Oxygenotherapy consists of a continuous administration of inhaled oxygen at a higher concentration than environmental air in order to ensure a better diffusion to the bloodstream.

2.2.1.Oxygen devices

There are different devices in which oxygen is contained that can be prescribed domiciliary to the patient according to his needs and way of life. They are the cylinders, liquid oxygen containers and the concentrators.

Cylinders contain gaseous oxygen and they are heavy and difficult to carry. They need to be refilled periodically, and though they are only a supply source in emergency cases and are not used daily, they are harder to use for some patients, especially the elder ones.

Liquid oxygen is stored in tanks at a temperature of -183° C, and depending on the individual's use, it may take from 5 to 7 days to run out. One advantage is that it can be carried in small backpacks, for those who need it to go out of home, having 3 or 4 hours of autonomy. Furthermore, there are continuous flow devices of that kind or pulsatile valve devices, that release oxygen only with the patient's inspiration, saving it and lasting longer. The inconveniences of these tanks are the risk or burns when manipulating it to refill it (liquid

oxygen is dangerously cold and any contact with the skin can produce a burn) and their high cost.

Concentrators extract oxygen from environmental air breaking it apart from air nitrogen through filters (see **annex 2**). They can be portable or static. The static ones are plugged to the electricity and so they do not need periodical refills and the portable ones have a battery source with limited lasting. These last ones can have a continuous (with a maximum of 3 litters/ minute) or a pulse administration, being the pulsatile form very useful to these active individuals with greater autonomy. Though they are cheaper than other devices, sometimes they might be loud, and the portable ones may not be enough for those patients who require higher flows of oxygen to hold the saturation levels up.

All of them must adjust the FiO_2 (inhaled oxygen concentration) and the O_2 flow (litters/ minute) given to the patient. Environmental air is at FiO_2 21% (0,21), so any oxygen prescribed must be at a superior concentration. The mechanism in which concentrators modify the FiO2 is exposed in annex 3.

Nowadays oxygen therapy is given at various concentrations to those who desaturate below 88% of the SpO_2 (oxyhaemoglobin) in a pulse oximetry during the 6mWT, to use it when executing challenging activities (walking to the supermarket, after eating or even in the shower or to dress up) or chronically to those whose basal oxygen saturation in pulse oximetry or arterial gasometry is SpO_2 below the threshold of chronic respiratory insufficiency (CRI), which is lower than 89%. To the latter, it must be prescribed a minimum use of 15 hours a day. (7)(11)(1).

2.2.2.Current evidence on the benefits of oxygenotherapy

The therapeutic indications and practices are based on poor evidence when it comes to IPF, since all studies on oxygenotherapy's impact on survival, quality of life and dyspnoea have proved a significant benefit only in patients with Chronic Obstructive Pulmonary Disease (COPD) and chronic respiratory insufficiency (CRI: SpO_2 <89% and PaO_2 <60 mmHg) (12). In fact, studies have shown that the benefits of oxygen in COPD patients diminish drastically when saturation is above 89%, finding no relevant difference between those treated with O_2 and those who are not (13)(3). Regarding the exertional dyspnoea, the only evidence of improvement is again in COPD patients, and it shows an increase of both distance and saturation levels in the 6mWT in a short term. In spite of that, when the SpO_2 in a 6mWT is <88% in any chronic respiratory disease, oxygen therapy can be prescribed to be used during exertional activities (14)(11).

Another indication for the prescription of oxygen is the nocturnal hypoxaemia below SpO_2 90% during at least 30% of the record taken by nocturnal pulse oximetry (CT90 >30%), especially when it comes with polycythaemia or signs of right heart failure(15)(16). The evidence on whether nocturnal O_2 brings a better sleep quality are limited (12)(1).

The use of palliative oxygen to control refractory dyspnoea secondary to neoplasia or a terminal process has been proved inferior to opioids (17)(18).

Table 5. Current indications for oxygen therapy administration.

TEST	BASAL O_2 BLOOD SATURATION	O_2 ADMINISTRATION
PULSE OXIMETRY or ARTERIAL GASOMETRY	SpO_2 < 89% / PaO2 < 60 mmHg (CRI) Or SpO2 89-95% / PaO2 55-60 mmHg + morbidities[1]	Continuous flow minimum 15 hours a day
6 MINUTES WALKING TEST	Mean SpO_2 < 88%	Continuous or pulsatile
NOCTURNAL POLYGRAPHY	Mean SpO_2 < 90% more than 30% of sleep (CT90 >30%)	Nocturnal[2]

1.Morbidities: Pulmonary Hypertension, Polycythaemia, Cor Pulmonale 2.Nocturnal oxygen must be adjusted to avoid CO_2 retention (1)(2)

2.2.3.Side effects of oxygenotherapy

Hypercapnia

It is an increment of carbon dioxide (CO_2) concentration in blood (CO_2 retention) caused mainly by the ventilatory/diffusion unbalance. An excess of inhaled oxygen generates hypercapnia by diminishing the breathing rate and causing an increased storage of CO_2. Since the respiratory rate is lower during the sleep, hypercapnia is more likely to happen during the night-time or in the morning, and nocturnal O_2 dose has to be adjusted to avoid it (1).

Pulmonary toxicity

Oxygen can cause direct lung injuries in focal or diffuse lung areas (both acute and chronic). It is more common to see such lesions in chronic high flow oxygen therapies, being the level of lung affection dose and exposure dependant.

Nasal mucosa irritation and contact eczema

Epistaxis, nasal congestion and mucosal irritation are possible side effects of chronic oxygenotherapy, as well as contact eczema.

Ignition and explosion risk

Liquid oxygen has been reported to provoke burns by contact though it is very uncommon. Explosion and fire risks are highly related to the persistence of smoking in those patients exposed to oxygenotherapy (1).

3. Justification

Nowadays the indications to prescribe oxygenotherapy in IPF and other diffuse interstitial lung diseases (DILDs) are based on scarce and low-quality evidence (4). Most guidelines acknowledge that the only studies found significant both clinically and statistically were carried out in patients with COPD, and they stated that oxygen helped them improve their quality of life and functional capacities solely in a stage of basal CRI (SpO_2 <89%/ PaO2< 60 mmHg)(1).

According to data reported by CatSalut, 12.558 people were using domiciliary oxygen therapy in December 2013 in Catalunya. That was a 6,7% more than 2012 and a 15,6% higher than in 2009.

Although being relatively innocuous, O_2 still has potentially grave side effects if an accurate control and follow up is not established on the patient. Among these adverse effects, hypercapnia (CO_2 retention) and pulmonary toxicity are the most threatening ones, with a considerable risk of compromising the patient's life. Furthermore, an inadequate manipulation of the O_2 delivering device may increase the risk of explosion, burn or ignition, especially when in contact with the smoking habit, persistent in some patients despite medical advice. Other minor undesired repercussions to O_2 are epistaxis, nasal congestion or irritation and contact skin eczema caused by the canulae. All in all, these should be taken into consideration when prescribing oxygenotherapy, and new significant evidence supporting or refuting that prescription would be of help to avoid an unnecessary exposition of the patient to such risks.

Moreover, the most commonly used devices are the static concentrator followed by the portable concentrator, and their prescription has gone up to a 25,3% and a 339,3% respectively since 2009, in detriment of the cylinders and liquid oxygen(14). Again, a study of the effects of this therapy on IPF could be of use to justify whether this spending is well invested or, on the contrary, we are wasting resources in treatments that do not present any benefit to our patients.

Unfortunately, prognosis in most IPF diagnosed subjects is poor, and the current treatment aims to slow down the progression of the disease, increasing the survival expectancy. Therefore, since there is no cure for it, the improvement in quality of life for those patients is crucial, and

to test the effectiveness of oxygen in that field could bring new knowledge of a better treatment that enables most subjects to carry on with their way of life for as long as possible.

4. Hypothesis

Does continuous domiciliary oxygen therapy present any benefit, either in functional respiratory capacities, quality of life or survival, in patients with idiopathic pulmonary fibrosis that have a blood SpO2 saturation between 89 and 95% in comparison to those who do not use it?

5. Objectives

5.1. Main objective

The aim of this study is to measure the effects of ambulatory oxygen therapy on patients with idiopathic pulmonary fibrosis who suffer moderate hypoxaemia (SpO_2 between 89-95%) and see if they present any benefit in their quality of life measured in EuroQol-5D-5L questionnaire (see **annex 1**) using three tools: EQ-5D index, Severity Index and Analogical Visual scale (AVS) in 2 years term.

5.2. Secondary objectives

- To evaluate the evolution of dyspnoeic sensation along the trial (2 years) through mMRC dyspnoea scale.
- To count the number of acute exacerbations provoked by the disease and the time to the first one.
- Number of hospitalisations due to any cause during the study
- To report a possible positive impact on survival rates in 2, 3 and 5 years

6. Design

This study is designed as a prospective, 2 years, multicentric, randomised, parallel and controlled clinical trial.

7. Sample selection

The size of the sample would be 358 subjects according to the inclusion criteria and after being filtered by the exclusion criteria assuming an α risc (error type I) of 0,05 and a β risc (error type II) of 0,20. The abandonment rate has been set on 10% of all participants.

That sample would be divided randomly into 2 groups of 179 participants, one of which would be the intervention group (they will receive continuous O_2) and the other the control group (no continuous O_2 will be prescribed to them). A third group of 97 individuals with CRI (basal

SpO2 <89%/ PaO_2 < 60 mmHg) will be observed assuming a precision assessment of +/- 0,20 units to evaluate their progress with continuous O_2.

The sample size for the three groups has been calculated with the help of online webpage calculator GRANMO.

8. Methods

At the beginning all participants with diagnosed mild to moderate IPF and a basal saturation of SpO_2 between 89 and 95% in a pulse oximetry during the day will be randomized in two groups. The intervention group will carry an ambulatory oxygen device at a flow of 2 litters per minute (l/min) a minimum of 16 hours a day for 2 years while the control group will carry no oxygen device and will breathe environmental air.

The primary outcome will be the participants quality of life (measured in EuroQol-5D-5L questionnaire)(see **annex1**) along the trial and secondary outcomes will be the number of hospitalisations, number of acute exacerbations and the time to the first one, the worsening of functional respiratory parameters and physical capacity (measured in respiratory tests, mMRC scale and 6 minutes walking test). Another secondary outcome to be measured in this trial will be the number of survivors at 2, 3 and 5 years after the beginning of oxygen administration (stated in the check-ups during the study and a final phone call to the patients in 5 years).

A third group with CRI (basal SpO2 <89%/ PaO_2< 60 mmHg) will be included in the study to analyse the same outcomes with no control group. An observational follow up of the progression these subjects receiving continuous O_2 will report new evidence of the course of these terminal stages of IPF.

To study the effects of oxygen in all participants, they will be distributed in the following groups:

- **Group 1**: patients with basal SpO_2 89-95% receiving O_2 at flow of 2 litters/minute a minimum of 16 hours a day (including night-time).
- **Group 2**: patients with basal SpO_2 89-95% that will not receive O2. In case some of these patients presented a nocturnal hypoxia of a mean SpO_2 <90% or a CT90 > 30% (SpO_2 <90% more than 30% of the sleep time) they will receive O_2 at 2 litters/ minute during sleep.
- **Group 3** (not compared to the rest): patients with basal SpO_2 <89% (with CRI) will all receive O2 at a minimum flow of 2 litters/minute a minimum of 16 hours including the night-time. That group will be studied as an observational progression.

- It will be taken into consideration to prescribe O_2 at an individualised flow during physical activity to any patients who desaturate SpO2 <90% during 1 minute at a 6mWT.

9.1. *Enrolment and inclusion criteria*

To participate in this trial all patients will require:

- A certified diagnose of IPF with a mild or moderate degree of severity.
- To be under 80 years old.
- A basal blood oxygen saturation of SpO_2 < 95%.
- FRT with a FVC between 50-80% and a DLco >35%.

As a multicentric randomised project, the enrolment will be consecutive. Patients under 80 years of age with a certified diagnose of IPF will be welcome to participate in this project. The degree of severity required to enter the study will be mild to moderate, with a forced vital capacity (FVC) between 50-80% and an alveolar diffusion DLco> 35% in an initial FRT. Despite not being specified as an inclusion critter, the degree of severity of the disease would require for all participants to follow an antifibrotic treatment.

9.2. Exclusion criteria

The following items will be considered as an impediment to join this project:

- More than 80 years of age.
- Diagnosed systemic diseases.
- Active smoking habit.
- Patients with a BMI > 30 with an Obesity-Hypopnea Syndrome.
- Hypercapnia ($PaCO_2$ > 45mmHg) detected by arterial gasometry.
- Diagnosed moderate or severe OSAS or patient treated with a CPAP.
- Diagnosed COPD simultaneous to the IPF.
- Diagnosed Asthma simultaneous to the IPF.

9.3. First visit

At the initial visit of this protocol, all participants will go through the following tests:

- Quality of life questionnaire ***EuroQol-5D-5L*** (see **annex 1**) will be passed on to all participants in order to have a standard to compare later. This set of items evaluates 5 dimensions of the patient's daily life (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) in 5 levels of severity (no problems (1), mild

problems (2), moderate problems (3), severe problems (4) and extreme problems/ incapacity (5)) combined with a final analogical visual scale (AVS) in which the patient has to choose at what level of welfare he/she has the day of the test, from 0 to 100 being the highest number the most welfare. It has been updated and tested for 30 years and has shown great utility in helping health professionals when taking decisions (19)(20).

- A ***High-Resolution Computed Tomography***, that most of them will already have from the visit in which IPF was diagnosed. That image will be a record of the initial situation of the individual and will be used to follow the radiological progress of the disease along the trial.
- ***Functional Respiratory Tests*** (*spirometry, CO diffusion, post-bronchodilator test and lung volumes*). That will be used to acknowledge the functional capacities of the patient at the beginning of the study and compare them to posterior check-ups. The initial FVC must be between 50-80% and the DLco >35%.
- A basal ***arterial gasometry*** will be required to make sure the patient meets the inclusion criteria of a resting hypoxaemia of SpO_2 89-95% and/or PaO_2 60-80 mmHg. Also it will be used to check that the $PaCO_2$ is within normal ranges (35-45 mmHg) to discard hypercapnia, and to have an initial record of the patients basal pH and HCO_3^- (to make sure there is no acidosis at the beginning of the trial, and thus see if it is developed later on along the progress).
- A ***6 minutes walking test*** (6mWT) will be performed to have a reference of the patient's capacity to compare to along the study. If the SpO2 at rest is > 95% but during this test the patient descends to <88%, then O_2 will be prescribed to him/her adjusted to personal needs during exercise.
- A ***Nocturnal Polygraphy*** will be performed to discard a concomitant OSAS as well as to report the oxygen saturation during the night.
- A ***blood analysis*** with a complete hemogram (including GSR and C-RP) hepatic enzymes (GOT, GPT, GGT, α-amylase, serum Bilirubin, Alkaline Phosphatase) and renal function indicators (Creatinine, Na^+, K^+ and serum Urea) and coagulation features (APTT and PT-INR).
- Dyspnoea ***mMRC*** *(modified Medical Research Council) scale* will be also passed on to report the degree of dyspnoea participants have at the beginning of the trial and see the progression along the study. This questionnaire is useful in assessing the baseline functional disability and dyspnoea affection of the patient, associating the level of impairment in a daily life caused by the suffered breathlessness (21). Although it is more frequently used in COPD to establish dyspnoea severity in the BODE index (22), it can be used in all respiratory diseases. mMRC is explained in the table below.

Table 6. mMRC scale

Grade	Symptom severity
0	Dyspnoea only with vigorous exercise
1	Dyspnoea when hurrying on ground level or walking up a slight hill
2	Walks slower than people of the same age because of dyspnoea, or needs to stop for breath when walking at own pace on ground level
3	Stops for breath after walking 100 yards (91 metres) or after a few minutes on ground level
4	Too breathless to leave the house or dyspnoea when dressing

9.4. Follow up and check-ups

All participants will be assigned a clinical check up every 6 months during the 2 years this trial will last. In every visit they will go through the following tests to report any changes or progress:

- Quality of life questionnaire ***EuroQol-5D-5L*** (see **annex 1**)
- Dyspnoea ***mMRC*** *(modified Medical Research Council) scale*
- *A* ***High-Resolution Computed Tomography***
- ***Functional respiratory tests*** (*spirometry, CO diffusion and lung volumes*)
- ***6 minutes Walking Test***
- ***Arterial gasometry***
- At every visit adherence to oxygen and daily hours of use of the device will be checked to assure a minimum use of 16 hours a day by the participants.
- A ***blood analysis*** will be conducted at least at the first visit after 6 months from the beginning in order to make sure that the antifibrotic treatment is well adjusted and no hepatic or renal damage is going unnoticed.

At year 2, 3 and 5 after the first day of oxygen administration a **telephonic call** will be made to all subjects to check the number of survivors at that time.

10. Statistical analysis

10.1. Variables

Independent variable/ Intervention

The prescribing of a minimum of 16 hours a day of continuous domiciliary O_2 at a flow of 2 litters/ minute for 2 years will be the independent variable of this trial. All devices will have a system to report the hours of use a subject does every day.

Dependant variables

1. Quality of life (measured in EuroQol-5D-5L questionnaire: EQ-5D index, Severity Index and AV scale). Continuous quantitative variable (see **annex 1**).
2. Dyspnoea sensation (measured in mMRC scale). Categorical quantitative variable.
3. Number of hospitalisations. Categorical quantitative variable.
4. Number of acute exacerbations of the disease. Categorical quantitative variable.
5. Time to the first acute exacerbation of the disease (days). Continuous quantitative variable.
6. Functional capacity evolution (measured in the 6mWT and RFT like spirometry, volumes and DLco). Continuous quantitative variables.
7. Radiological progression stated by HRCT. Qualitative categorical variable. (better/ stable/ worse)
8. Survival rate at the end of the study and in 5 years determined by a telephonic call. Continuous quantitative variable.

10.2. EuroQol-5D-5L interpretation, analysis and results

The results of this questionnaire will be measured in three different ways: in EQ-5D index, a descriptive mean from 0 to 1 of the levels of the 5 dimensions adjusted to objective values (table 6) specifically given in every country(23) (coefficients studied in Spain will be our references)(24)(25). This index is adjusted to a particular country, taking into account the social perception of each category and how important they are considered in that society. Therefore, coefficients vary from region to region. The results can go from 1 (11111) to -0,225 (55555) which is a status considered worst than death. Each level of severity of each dimension is paired to a value, and they must be subtracted to the initial value of 1. If the global status is higher than 11111, an additional subtraction of the Constant value must be done. An example would be a patient whose own health valuation in EQ-5D-5L was 11131. Then we would have that the global **EQ-5D index** would be (1 -0,0074356 (Constant) – 0,1017094 (Pain level 4) = 0,890855 Index).

Table 7. Adjusted coefficients for EQ-5D-5L in Spain(24)(25).

Category	Levels	Values
Constant (any category)	> 1	-0.0074356
Mobility	2	-0.084492
	3	-0.0988167
	4	-0.2283521
	5	-0.2879821
Daily activities	2	-0.0533192
	3	-0.0587116
	4	-0.1307201
	5	-0.1343742
Personal care	2	-0.0562838
	3	-0.0564156
	4	-0.1529359
	5	-0.1688327
Pain / Discomfort	2	-0.0779462
	3	-0.1017094
	4	-0.2169955
	5	-0.322017
Anxiety / Depression	2	-0.0853898
	3	-0.1293305
	4	-0.2505774
	5	-0.3035584

Another way to present the results will be in a **Severity Index** (SI) or Sum Score(26), which is the sum of the absolute levels (from 1 to 5) of all categories minus 5, which gives a range of values between 0 (11111-5) to 20 (55555-5)(25). It will then be multiplied 5 times and it will express a range from the absence of health problems with a 0 to the worst health perception with a 100. Finally, the AVS scale will give a simple visual perception of the health status in a concrete instant(24)(25).

10.3. Descriptive analysis

The one qualitative variable (HRCT progression) and the survival rate at 2, 3 and 5 years will be expressed in compared proportions/ percentages between the Group 1 (intervention), Group 2 (control) and Group 3 (CRI group).

All quantitative variables with a symmetric distribution will be shown as compared means with their standard deviation (SD) whilst all those with an asymmetric distribution will be expressed as a mean with their interquartile range (IQR).

10.4. Comparison of the groups and inference

All comparisons will be established and expressed according to a temporal coherence, and we intend to analyse and express all data obtained in every check-up visit to stratify the results in time events.

Regarding the inference in qualitative variables (HRCT progression), all categorical variables and survival rate they will be compared between groups intervention and control in proportions and they will be analysed using a Chi-Square (x^2). Means of the rest of continuous variables will be compared using a Students t- test.

Regressions will be used to assess the association between the independent variable (O_2) and the dependant variables. For the continuous variables we will use a linear regression whereas for the discrete dependent variables Poisson regression will measure relative risk and confidence intervals.

The results will be statistically significant when the value of $p < 0,01$ and all results within a confidence interval of 80% will be taken into consideration. The minimal relevant clinical significance has been set at an improvement of 0,20 between groups.

10.5. Strengths and limitations

The following limitations may interfere with the extraction of conclusions of this trial:

- On the one hand, due to the lack of a double-blinding assignation of subjects to each group, those receiving oxygen will be exposed to the placebo effect, which could influence their perception of improvement or worsening of their quality of life and dyspnoeic sensation (expressed in subjective questionnaires). On the other hand, the devices have inconveniencies like having to carry an extra weight around to leave the house, the social stigma of the device canulae that could bother some patients or some minor side effects of this therapy, exposed before. Therefore, it is considered that global quality of life will be evaluated as a whole by the participants, reducing the impact of the placebo effect. Furthermore, to reduce this subjective perception secondary objectives will be studied like the number of hospitalisations, the number of acute exacerbations and the time to the first one, as well as global survival which will show more objectively the impact of oxygen in the quality of life.
- There can be an information bias as this trial is based in an ambulatory intervention whose compliance estimators have no control of. To reduce that chance the current oxygen devices can report online even weekly the number of hours a participant uses them, thus having a record of the compliance.

- Since IPF is still an illness with poor prognosis the risk of losses along the trial is considerable, and that could damage the external validity (attrition bias). That is why this study is multicentric.

11.Clinical and health care impact

Nowadays IPF is a disease with a progressive course to a terminal respiratory insufficiency that cannot be reversed. The results of this trial could bring light to the existent knowledge about the effectiveness of oxygen in improving, or at least maintaining, the way and quality of life of these patients.

Moreover, oxygen is widely used today and its prescription has to be reassured and supported by evidence in the illness that is being treated. Since all significant studies are based in COPD there is a wide range of diseases in which this therapy is used without proper certainty.

12. Ethical discussion

This trial will be designed according to the principles of the *Helsinki Declaration of Ethical Principles for Medical Research Involving Human Subjects* established in 1964 and lately revised in October 2013.

- All subjects will be treated according to the latest evidence and guidelines, with proper antifibrotic treatment for the IPF, symptomatic cares and a close follow up on the progression and unexpected events that may occur.
- Those patients with basal CRI or severe hypoxaemia at rest (Group 3) will receive ambulatory oxygen despite the non-existent evidence regarding IPF, because the implications of not treating grave hypoxia could be fatal and therefore the ethical burden of this risk is not acceptable.
- Since there is not enough evidence to determine whether patients with IPF and mild hypoxaemia may benefit from continuous oxygenotherapy, the control group of this study will not be treated unethically by not receiving oxygen, for the main purpose of this trial is to reinforce that evidence and they will be closely checked in order to be able to change any therapeutic measures (including the implementation of a continuous oxygen prescription for them) if the course of the disease worsens.

13. Study chronogram and work plan

YEAR		MONTH	STAGE	
2019	Study Year 0	September - November	**Study design**	STUDY PREPARATION
		December	**Ethical evaluation & Trial approval**	
2020		January		
		February	**Multiple centres coordination**	
		March - September	**Enrolment of participants**	
		October	**1st visit & Informed consent**	INTERVENTION & DATA COLLECTION
2021	Study Year 1	April	**1st Control check up**	
		October	**2nd Control check up**	
2022	Study Year 2	April	**3rd Control check up**	
	Study Year 3	October	**4th Control check up** **Last follow-up visit**	
2023		October	**1st Telephonic call for survival check up**	SURVIVL CHECK & STATISTICAL ANALYSIS
2024	Study Year 4	October	*	
2025	Study Year 5	October	**2nd Telephonic call for survival check up** **End of data collection**	
	Year 6	November - December	**Statistical analysis**	
2026		January	**Official publication**	

14. Budget

N= 358 Group 1: 179 Group 2: 179 Group 3: 97	**Individual cost (€)**	**Number of participants using it**	**Number of uses (days)**	**TOTAL COST (€)**
Thorax HRCT	204	358 + 97 (455)	5	464.100
RFT (spirometry, volumes, post-bronchodilator test and DLco)	236	358 + 97 (455)	5	536.900
Arterial gasometry (PaO_2, $PaCO_2$, pH, SpO_2, $paHCO_3^-$)	2,59	358 + 97 (455)	5	5.892,25
6MWT	15	358 + 97 (455)	5	34.125
Nocturnal Polygraphy	414	358	1	148.212
Oxygen devices	Static 3,3 / day (25%) Portable 7 / day (75%)	179 + 97 (276)	730	1.223.991
Blood analysis Complete hemogram and GSR and C-RP Hepatic enzymes (GOT, GPT, Alkaline Phosphatase, GGT, α-Amylase, Bilirubin) Renal functionalism (Creatinine, Na^+, K^+, Urea) Haemostasis (APTT, PT-INR)	8,63	358 + 97 (455)	5	19.633,25
TOTAL				**2.432.853,50** €

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16.Annexes

16.1. Annex 1: EuroQol-5D-5L Questionnaire

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discom ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

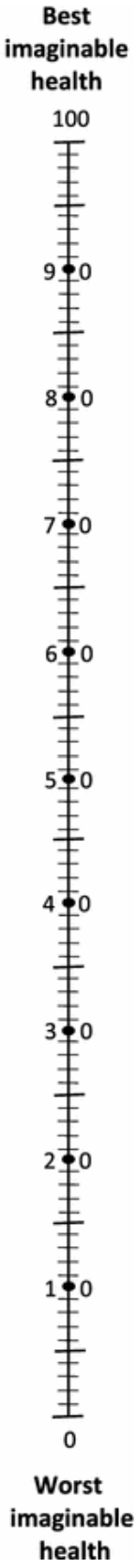
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

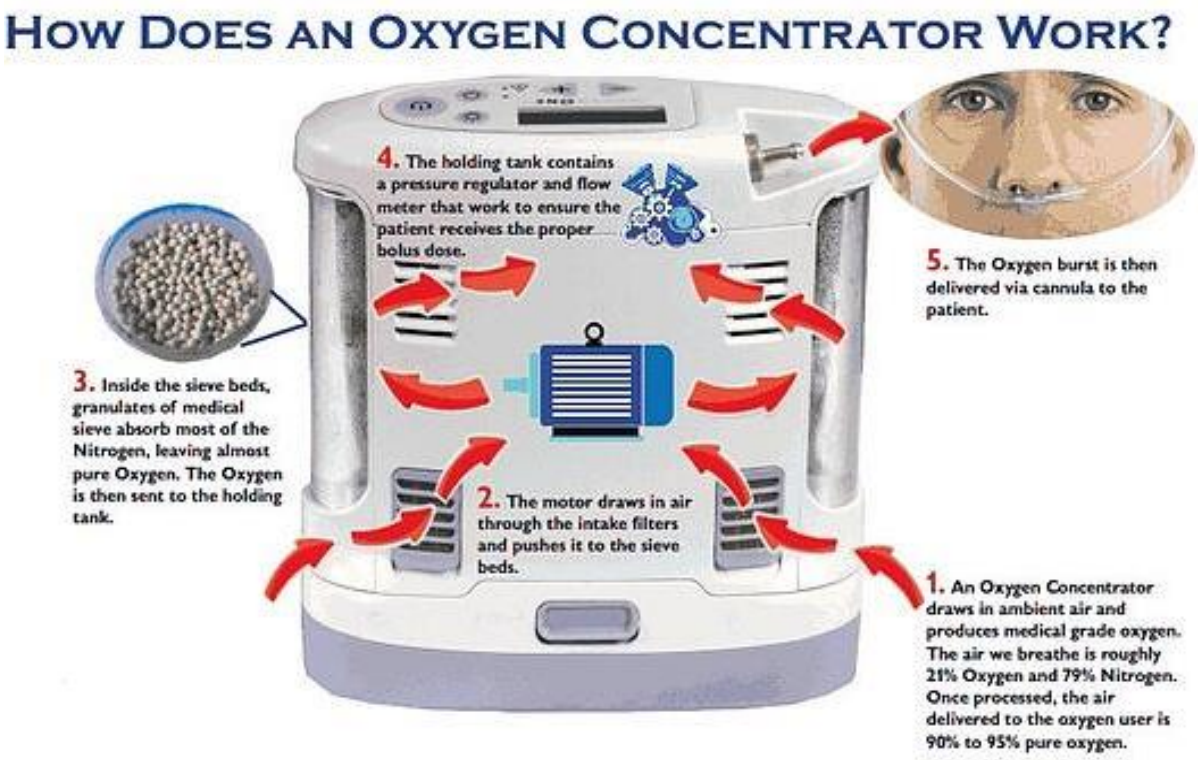
VALUING YOUR OWN HEALTH TODAY

- We would like to know how good or bad your health is TODAY
- This scale is numbered from 0 to 100
- 100 means the best health you can imagine
- 0 means the worst health you can imagine

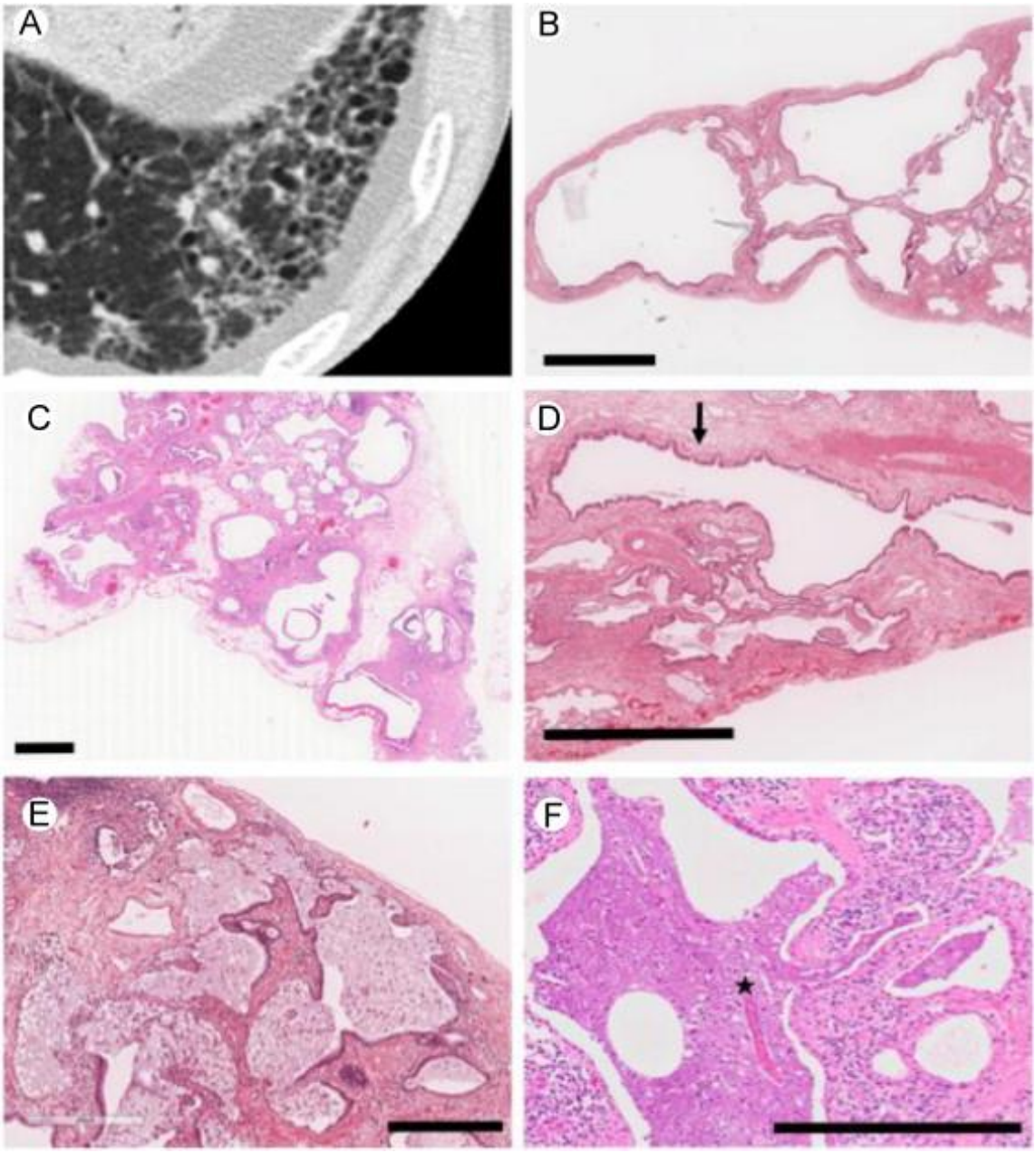
Please write in this box the number between 0 and 100 that you think best indicates YOUR HEALTH TODAY



16.2. Annex 2: Oxygen concentrators mechanical functioning



16.3. Annex 3: Radiological and histological honeycombing pattern



Honeycomb cysts seen by radiologists (A) and pathologists (B, C, D, E, F). **A)** Axial HRCT of left medial lobule. Subpleural bronchiectasis, thick walls traction atelectasis can be seen especially in the posterior part of the lung, forming a honeycombing pattern. Radiologically the honeycomb cysts are a cluster of thick-walled cysts with 0,5-1 cm of diameter or more(10). **B)** Histological cut obtained by SLB from the patient shown in picture (A) where homogeneous cysts can be seen. **C)** Another cut showing a more heterogeneous pattern with a combination of cysts, fibrotic areas connecting their walls (pseudoseptum) and blood vessels. **D)** Example of a traction bronchiolectasis produced by the effect of the surrounding fibrotic tissue where smooth muscle cells can still be seen (black arrow) around the terminal bronchioles. That finding can only be observed histologically in a microscope. **E)** Microscopic honeycombing seen at an early stage. This pattern is initially lined by the alveolar columnar ciliated epithelium and tends to be filled with mucin with different features indicating an acute or subacute inflammatory process. **F)** Image of multiple microscopic cysts some of them filled with proteinous material (black asterisk) which can be taken for an alveolar proteinosis. Scale bars (B-F respectively): 2mm, 1mm, 2mm, 100μm and 100 μm(10).