



HAL
open science

Insight into the relationship between forced vital capacity and transfer factor of the lung for carbon monoxide in patients with idiopathic pulmonary fibrosis

Salomé Nussbaum

► **To cite this version:**

Salomé Nussbaum. Insight into the relationship between forced vital capacity and transfer factor of the lung for carbon monoxide in patients with idiopathic pulmonary fibrosis. Human health and pathology. 2021. dumas-03601218

HAL Id: dumas-03601218

<https://dumas.ccsd.cnrs.fr/dumas-03601218v1>

Submitted on 8 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

AVERTISSEMENT

Ce document est le fruit d'un long travail approuvé par le jury de soutenance.

La propriété intellectuelle du document reste entièrement celle du ou des auteurs. Les utilisateurs doivent respecter le droit d'auteur selon la législation en vigueur, et sont soumis aux règles habituelles du bon usage, comme pour les publications sur papier : respect des travaux originaux, citation, interdiction du pillage intellectuel, etc.

Il est mis à disposition de toute personne intéressée par l'intermédiaire de [l'archive ouverte DUMAS](#) (Dépôt Universitaire de Mémoires Après Soutenance).

Si vous désirez contacter son ou ses auteurs, nous vous invitons à consulter la page de DUMAS présentant le document. Si l'auteur l'a autorisé, son adresse mail apparaîtra lorsque vous cliquerez sur le bouton « Détails » (à droite du nom).

Dans le cas contraire, vous pouvez consulter en ligne les annuaires de l'ordre des médecins, des pharmaciens et des sages-femmes.

Contact à la Bibliothèque universitaire de Médecine Pharmacie de Grenoble :

bump-theses@univ-grenoble-alpes.fr

Année : 2021

**CAPACITE VITALE FORCEE ET DIFFUSION DU MONOXYDE DE CARBONE
DANS LA FIBROSE PULMONAIRE IDIOPATHIQUE : CE QUE CHANGE
L'UTILISATION DES NORMES GLI**

THÈSE
POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

SPÉCIALITÉ : PNEUMOLOGIE

Par **NUSSBAUM Salomé**

[Données à caractère personnel]

THÈSE SOUTENUE PUBLIQUEMENT À LA FACULTÉ DE MÉDECINE DE
GRENOBLE

Le 03/09/2021

DEVANT LE JURY COMPOSÉ DE :

Président du jury :

M. Christophe Pison

Membres :

M. Bruno DEGANO, directeur de thèse

M. Bernard AGUILANIU

M. Sébastien QUETANT

M. Loïc FALQUE

L'UFR de Médecine de Grenoble n'entend donner aucune approbation ni improbation aux opinions émises dans les thèses ; ces opinions sont considérées comme propres à leurs auteurs.

Doyen de la Faculté : Pr. Patrice MORAND

Année 2020-2021

ENSEIGNANTS DE L'UFR DE MEDECINE

CORPS	NOM-PRENO	Discipline universitaire
PU-PH	ALBALADEJO Pierre	Anesthésiologie-réanimation et médecine péri-opératoire
PU-PH	APTEL Florent	Ophtalmologie
PU-PH	ARVIEUX-BARTHELEMY Catherine	Chirurgie viscérale et digestive
PU-PH	BAILLET Athan	Rhumatologie
PU-PH	BARONE-ROCHETTE Gilles	Cardiologie
PU-PH	BAYAT Sam	Physiologie
MCF Ass.MG	BENDAMENE Farouk	Médecine Générale
PU-PH	BENHAMOU Pierre-Yves	Endocrinologie, diabète et maladies métaboliques
PU-PH	BERGER François	Biologie cellulaire
MCU-PH	BIDART-COUTTON Marie	Biologie cellulaire
PU-PH	BLAISE Sophie	Chirurgie vasculaire ; médecine vasculaire
PR Ass. Méd.	BOILLOT Bernard	
MCU-PH	BOISSET Sandrine	Bactériologie-virologie ; Hygiène hospitalière
PU-PH	BONAZ Bruno	Gastroentérologie ; hépatologie ; addictologie
PU-PH	BONNETERRE Vincent	Médecine et santé au travail
PU-PH	BOREL Anne-Laure	Nutrition
PU-PH	BOSSON Jean-Luc	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	BOTTARI Serge	Biologie cellulaire
PR Ass.MG	BOUCHAUD Jacques	Médecine Générale
PU-PH	BOUGEROL Thierry	Psychiatrie d'adultes
PU-PH	BOUILLET Laurence	Médecine interne ; gériatrie et biologie du vieillissement ; addictologie
MCU-PH	BOUSSAT Bastien	Epidémiologie, économie de la santé et prévention
PU-PH	BOUZAT Pierre	Anesthésiologie-réanimation et médecine péri-opératoire
PU-PH émérite	BRAMBILLA Christian	Pneumologie
PU-PH émérite	BRAMBILLA Elisabeth	Anatomie et cytologie pathologiques
MCU-PH	BRENIER-PINCHART Marie Pierre	Parasitologie et mycologie
PU-PH	BRICAULT Ivan	Radiologie et imagerie médicale
PU-PH	BRICHON Pierre-Yves	Chirurgie thoracique et cardiovasculaire
MCU-PH	BRIOT Raphaël	Thérapeutique-médecine de la douleur ; Addictologie
PU-PH émérite	CAHN Jean-Yves	Hématologie
PU-PH émérite	CARPENTIER Patrick	Chirurgie vasculaire, médecine vasculaire
PR Ass.MG	CARRILLO Yannick	Médecine Générale
PU-PH	CESBRON Jean-Yves	Immunologie
PU-PH	CHABARDES Stephan	Neurochirurgie
PU-PH	CHABRE Olivier	Endocrinologie, diabète et maladies métaboliques
PU-PH	CHAFFANJON Philippe	Anatomie
MCF Ass.MG	CHAMBOREDON Benoît	Médecine Générale
PU-PH	CHARLES Julie	Dermato-vénérologie
MCF Ass.MG	CHAUVET Marion	Médecine Générale
PU-PH	CHAVANON Olivier	Chirurgie thoracique et cardiovasculaire

CORPS	NOM-PRENOM	Discipline universitaire
PU-PH	CHIQUET Christophe	Ophtalmologie
PU-PH	CHIRICA Mircea	Chirurgie viscérale et digestive
PU-PH	CINQUIN Philippe	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	CLAVARINO Giovanna	Immunologie
PU-PH	COHEN Olivier	Histologie, embryologie et cytogénétique
PU-PH	COURVOISIER Aurélien	Chirurgie infantile
PU-PH	COUTTON Charles	Génétique
PU-PH	COUTURIER Pascal	Médecine interne ; gériatrie et biologie du vieillissement ; addictologie
PU-PH	CRACOWSKI Jean-Luc	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
PU-PH	DEBATY Guillaume	Médecine d'Urgence
PU-PH	DEBILLON Thierry	Pédiatrie
PU-PH	DECAENS Thomas	Gastroentérologie ; hépatologie ; addictologie
PR Ass. Méd.	DEFAYE Pascal	Cardiologie
PU-PH	DEGANO Bruno	Pneumologie ; addictologie
PU-PH	DEMATTEIS Maurice	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
PU-PH émérite	DEMONGEOT Jacques	Biostatistiques, informatique médicale et technologies de communication
MCU-PH	DERANSART Colin	Physiologie
PU-PH	DESCOTES Jean-Luc	Urologie
PU-PH	DETANTE Olivier	Neurologie
MCU-PH	DIETERICH Klaus	Génétique
MCU-PH	DOUTRELEAU Stéphane	Physiologie
MCU-PH	DUMESTRE-PERARD Chantal	Immunologie
PU-PH	EPAULARD Olivier	Maladies infectieuses ; Maladies tropicales
PU-PH	ESTEVE François	Biophysique et médecine nucléaire
MCU-PH	EYSSERIC Hélène	Médecine légale et droit de la santé
PU-PH	FAUCHERON Jean-Luc	Chirurgie viscérale et digestive
MCU-PH	FAURE Julien	Biochimie et biologie moléculaire
PU-PH	FERRETTI Gilbert	Radiologie et imagerie médicale
PU-PH	FEUERSTEIN Claude	Physiologie
PU-PH	FONTAINE Éric	Nutrition
PU-PH	FRANCOIS Patrice	Epidémiologie, économie de la santé et prévention
MCU-MG	GABOREAU Yoann	Médecine Générale
PU-PH	GARBAN Frédéric	Hématologie ; Transfusion
PU-PH	GAUDIN Philippe	Rhumatologie
PU-PH	GAVAZZI Gaétan	Médecine interne ; gériatrie et biologie du vieillissement ; addictologie
PU-PH	GAY Emmanuel	Neurochirurgie
MCU-PH	GILLOIS Pierre	Biostatistiques, informatique médicale et technologies de communication
PU-PH	GIOT Jean-Philippe	Chirurgie plastique, reconstructrice et esthétique ; Brûlologie
MCU-PH	GRAND Sylvie	Radiologie et imagerie médicale
PU-PH émérite	GRIFFET Jacques	Chirurgie infantile
MCU-PH	GUZUN Rita	Nutrition
PU-PH	HAINAUT Pierre	Biochimie et biologie moléculaire
PU-PH émérite	HALIMI Serge	Nutrition
PU-PH	HENNEBICQ Sylviane	Biologie et médecine du développement et de la reproduction ; gynécologie médicale
PU-PH	HOFFMANN Pascale	Gynécologie-obstétrique ; gynécologie médicale
PU-PH émérite	HOMMEL Marc	Neurologie
PU-MG	IMBERT Patrick	Médecine Générale

CORPS	NOM-PRENUM	Discipline universitaire
PU-PH émérite	JOUK Pierre-Simon	Génétique
PU-PH	KAHANE Philippe	Physiologie
MCU-PH	KASTLER Adrian	Radiologie et imagerie médicale
PU-PH	KRAINIK Alexandre	Radiologie et imagerie médicale
PU-PH	LABARERE José	Epidémiologie, économie de la santé et prévention
MCU-PH	LABLANCHE Sandrine	Endocrinologie, diabète et maladies métaboliques
MCU-PH	LANDELLE Caroline	Bactériologie – virologie ; Hygiène hospitalière
PU-PH	LANTUEJOL Sylvie	Anatomie et cytologie pathologiques
PR Ass. Méd.	LARAMAS Mathieu	Cancérologie ; radiothérapie
MCU-PH	LARDY Bernard	Biochimie et biologie moléculaire
MCU - PH	LE GOUELLEC LE PISSART Audrey	Biochimie et biologie moléculaire
PU-PH	LECCIA Marie-Thérèse	Dermato-vénérologie
MCF Ass.MG	LEDOUX Jean-Nicolas	Médecine Générale
PU-PH émérite	LETOUBLON Christian	Chirurgie viscérale et digestive
PU-PH	LEVY Patrick	Physiologie
PU-PH	LONG Jean-Alexandre	Urologie
MCU-PH	LUPO Julien	Bactériologie-virologie ; Hygiène hospitalière
PU-PH	MAIGNAN Maxime	Médecine d'urgence
PU-PH	MAITRE Anne	Médecine et santé au travail
MCU-PH	MALLARET Marie-Reine	Bactériologie – virologie ; Hygiène hospitalière
MCU-PH	MARLU Raphaël	Hématologie ; Transfusion
PR Ass. Méd.	MATHIEU Nicolas	Gastroentérologie ; hépatologie ; addictologie
MCU-PH	MAUBON Danièle	Parasitologie et mycologie
PU-PH	MAURIN Max	Bactériologie-virologie ; Hygiène hospitalière
MCU-PH	MC LEER Anne	Histologie, embryologie et cytogénétique
MCU-PH	MONDET Julie	Histologie, embryologie et cytogénétique
PU-PH	MORAND Patrice	Bactériologie-virologie ; Hygiène hospitalière
PU-PH	MOREAU-GAUDRY Alexandre	Biostatistiques, informatique médicale et technologies de communication
PU-PH	MORO Elena	Neurologie
PU-PH	MORO-SIBILOT Denis	Pneumologie ; addictologie
MCU-PH	MORTAMET Guillaume	Pédiatrie
PU-PH	MOUSSEAU Mireille	Cancérologie ; radiothérapie
PU-PH émérite	MOUTET François	Chirurgie plastique, reconstructrice et esthétique ; brûlologie
MCF Ass.MG	ODDOU Christel	Médecine Générale
PR Ass. Méd.	ORMEZANO Olivier	Cardiologie
MCU-PH	PACLET Marie-Hélène	Biochimie et biologie moléculaire
PU-PH	PAILHE Régis	Chirurgie orthopédique et traumatologie
PU-PH	PALOMBI Olivier	Anatomie
PU-PH	PARK Sophie	Hématologie ; Transfusion
PU-PH	PASSAGGIA Jean-Guy	Anatomie
PR Ass.MG	PAUMIER-DESBRIERES Françoise	Médecine Générale
PU-PH	PAYEN DE LA GARANDERIE Jean-François	Anesthésiologie-réanimation et médecine péri-opératoire
MCU-PH	PAYSANT François	Médecine légale et droit de la santé
MCU-PH	PELLETIER Laurent	Biologie cellulaire
PU-PH	PELLOUX Hervé	Parasitologie et mycologie
PU-PH	PEPIN Jean-Louis	Physiologie
PU-PH	PERENNOU Dominique	Médecine physique et de réadaptation

CORPS	NOM-PRENOM	Discipline universitaire
PU-PH	PERNOD Gilles	Chirurgie vasculaire ; Médecine vasculaire
PU-PH	PIOLAT Christian	Chirurgie infantile
PU-PH	PISON Christophe	Pneumologie ; Addictologie
PU-PH	PLANTAZ Dominique	Pédiatrie
PU-PH	POIGNARD Pascal	Bactériologie-virologie ; Hygiène hospitalière
PU-PH	POLACK Benoît	Hématologie ; Transfusion
PU-PH	POLOSAN Mircea	Psychiatrie d'adultes ; Addictologie
PU-PH	RAMBEAUD Jean-Jacques	Urologie
PU-PH	RAY Pierre	Biologie et médecine du développement et de la reproduction ; gynécologie médicale
PR Ass. Méd.	RECHE Fabian	Chirurgie viscérale et digestive
MCU-PH	RENDU John	Biochimie et biologie moléculaire
MCU-PH émérite	RIALLE Vincent	Biostatistiques, informatique médicale et technologies de communication
PU-PH	RIETHMULLER Didier	Gynécologie-obstétrique ; gynécologie médicale
PU-PH	RIGHINI Christian	Oto-rhino-laryngologie
PU-PH émérite	ROMANET Jean Paul	Ophtalmologie
PU-PH	ROSTAING Lionel	Néphrologie
PU-PH	ROUSTIT Matthieu	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
MCU-PH	ROUX-BUISSON Nathalie	Biochimie et biologie moléculaire
PR Ass.MG	ROYER DE VERICOURT Guillaume	Médecine Générale
PU-PH émérite	SARAGAGLIA Dominique	Chirurgie orthopédique et traumatologie
MCU-PH	SATRE Véronique	Génétique
PU-PH	SAUDOU Frédéric	Biologie cellulaire
PU-PH	SCHMERBER Sébastien	Oto-rhino-laryngologie
PU-PH	SCHWEBEL Carole	Médecine intensive-réanimation
PU-PH	SCOLAN Virginie	Médecine légale et droit de la santé
MCU-PH	SEIGNEURIN Arnaud	Epidémiologie, économie de la santé et prévention
PU-PH émérite	STAHL Jean-Paul	Maladies infectieuses ; Maladies tropicales
PU-PH	STANKE Françoise	Pharmacologie fondamentale ; pharmacologie clinique ; addictologie
MCU-PH	STASIA Marie-José	Biochimie et biologie moléculaire
PU-PH	STURM Nathalie	Anatomie et cytologie pathologiques
PU-PH	TAMISIER Renaud	Physiologie
PU-PH	TERZI Nicolas	Médecine intensive-réanimation
PU-PH	THEVENON Julien	Génétique
MCU-PH	TOFFART Anne-Claire	Pneumologie ; Addictologie
PU-PH	TONETTI Jérôme	Chirurgie orthopédique et traumatologie
PU-PH	TOUSSAINT Bertrand	Biochimie et biologie moléculaire
PU-PH	VALMARY-DEGANO Séverine	Anatomie et cytologie pathologiques
PU-PH	VANZETTO Gérard	Cardiologie
PU-PH	VUILLEZ Jean-Philippe	Biophysique et médecine nucléaire
PU-PH	WEIL Georges	Epidémiologie, économie de la santé et prévention
PU-PH	ZAOUI Philippe	Néphrologie
PU-PH émérite	ZARSKI Jean-Pierre	Gastroentérologie ; hépatologie ; addictologie

PU-PH : Professeur des Universités - Praticiens Hospitaliers
 MCU-PH : Maître de Conférences des Universités - Praticiens Hospitaliers
 PU-MG : Professeur des Universités de Médecine Générale
 MCU-MG : Maître de Conférences des Universités de Médecine Générale
 PR Ass. Méd. : Professeur des Universités Associé de Médecine
 PR Ass.MG : Professeur des Universités Associé de Médecine Générale
 MCF Ass.MG : Maître de Conférences Associé de Médecine Générale

Résumé en français

Contexte : CVF et DL_{CO} sont les paramètres physiologiques les plus utilisés pour l'évaluation des patients porteurs d'une fibrose pulmonaire idiopathique (FPI). Ils sont exprimés en pourcentage d'une valeur de référence ou en Z-score, et l'utilisation des équations du Global Lung Initiative (GLI) est recommandée depuis peu. Les objectifs étaient de décrire la relation entre CVF et DL_{CO}, et d'évaluer l'influence du changement des valeurs de référence sur la décision médicale, notamment concernant la sélection des candidats à la transplantation pulmonaire.

Méthode : nous avons inclus tous les sujets de la cohorte COLIBRI-PID porteurs d'une FPI. Pour chacun, une mesure de DL_{CO} et une mesure de CVF ont été recueillies.

Résultats : cette observation transversale de 248 patients avec un large éventail de sévérité, a permis de montrer la relation non linéaire entre CVF et DL_{CO}. Ces résultats sont susceptibles de caractériser l'évolution de la CVF et de la DLCO lorsque la maladie progresse, pour un patient donné : on pourrait alors identifier une première phase de déclin de la DL_{CO} avec une CVF plutôt stable, puis une phase plus tardive où ces deux paramètres chutent ensemble. 17 patients ont changé de groupe pour être adressés vers un centre de transplantation pulmonaire en utilisant les équations GLI à la place des anciennes normes. Les valeurs limites considérées par le consensus de transplantation pulmonaire étaient de 40 % pour la DLCO ou 80 % pour la CVF.

Conclusion : La DL_{CO} semble essentielle à l'évaluation des formes de FPI à CVF préservée. L'utilisation de GLI est un plus sensible que les normes plus anciennes pour sélectionner les candidats à la transplantation pulmonaire.

Titre en anglais

Insight into the relationship between forced vital capacity and transfer factor of the lung for carbon monoxide in patients with idiopathic pulmonary fibrosis.

Résumé en anglais

Background : FVC and DL_{CO} are the most useful physiological parameters to assess idiopathic pulmonary fibrosis (IPF). They are expressed as percentage of reference value or Z-score, and the use of Global Lung Initiative (GLI) equations is now recommended. The objectives were to describe the relationship between FVC and DL_{CO} , and to assess the influence of the change in reference values on medical decision, namely regarding the selection of lung transplant candidates.

Methods : we included all subjects diagnosed with IPF from the cohort COLIBRI-ILD. Measurements of FVC and DL_{CO} performed at the same time were collected for each patient.

Results : in 248 IPF patients with a broad range of severity, this transversal observation highlighted the nonlinear relationship between FVC and DL_{CO} . Those results could allow us to characterise the course of FVC and DL_{CO} throughout disease progression for a given patient. In the first stages, FVC would remain steady while DL_{CO} would drop. In contrast, both would decline in the last stages. 17 patients switch group to be referred to a lung transplant center when we use GLI instead of the older standards, with the cut-off limit of 40 % for DL_{CO} or 80 % for FVC.

Conclusion : DL_{CO} seems essential in monitoring the IPF forms when FVC is preserved. The use of GLI is little more sensitive than older standards to select lung transplant candidates.

Insight into the relationship between forced vital capacity and transfer factor of the lung for carbon monoxide in patients with idiopathic pulmonary fibrosis.

ABBREVIATIONS

ATS: American Thoracic Society

ECSC: European Community for Steel and Coal

FVC: Forced Vital Capacity

GLI: Global Lung function Initiative

HRCT: High Resolution Computed Tomography

ILD: Interstitial Lung Disease

IPF: Idiopathic Pulmonary Fibrosis

LLN: Lower Limit of Normal

RV: Residual Volume

SD: Standard Deviation

TLC: Total Lung Capacity

TLCO: Transfer factor of the Lung for Carbon monoxide

UIP: Usual Interstitial Pneumonia

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and life-threatening interstitial lung disease characterized by interstitial inflammation, excess production of extracellular matrix and pulmonary vascular remodelling leading to progressive increase in elastic recoil and impaired gas exchange [1,2]. In patients, reliable non-invasive measurements that assess severity of lung involvement are needed at diagnosis and during follow-up in order to refine prognostic evaluation and allow accurate therapeutic management of IPF [3]. Forced vital capacity (FVC) and transfer of the lung for carbon monoxide (TLCO) are the two most widely non-invasive measurements used for that purpose. FVC has been used for many decades as the main criterion to assess disease severity, disease progression and treatment efficacy [4]. FVC is used in IPF because it is supposed to quantify pulmonary restriction [4]. Nevertheless, it is well-known that up to half patients with confirmed IPF have preserved FVC at diagnosis [5] because when the increase of lung elastic recoil is mild (i.e., in the initial stages of IPF), total lung capacity (TLC) and residual volume (RV) decrease but FVC remains normal [6]. It is only at later stages, when lung fibrosis and elastic recoil worsen, that the FVC significantly decreases. Although it is less frequently used than FVC to assess IPF severity and progression in clinical studies [7], TLCO has the strongest correlation with the morphologic extent of the disease [8,9] and outperforms FVC as an individual prognostic marker in IPF [10]. TLCO is the product of two separate but simultaneous measurements, the rate of uptake of CO from alveolar gas (KCO) and the alveolar volume (VA). As such, TLCO is a non-specific test that reflects not only pulmonary vascular destruction and alveolo-capillary membrane abnormality but also loss of lung volume. Surprisingly, to the best of our knowledge, the relationship between FVC and TLCO in IPF has not been extensively studied.

For medical decision in patients with IPF, percentages of predicted values (instead of rough values) are used to express results of FVC and TLCO, highlighting the crucial importance of robust, relevant and reliable reference equations [11]. The new reference equations proposed by the Global Lung Initiative (GLI) for FVC and for TLCO, based on a large sample of normal subjects [12,13], have been adopted by many respiratory societies [14]. It has been reported that using the GLI equations for FVC and TLCO substantially modifies eligibility for treatment with nintedanib or pirfenidone in IPF [15,16]. Another critical endpoint in IPF patients is the timing of referral for lung transplantation, with current recommendations stating that IPF patients should be considered for transplantation when FVC is less than 80% of predicted value and/or TLCO is less than 40% of predicted value using “old” reference equations [17]. What adoption of the GLI reference equations change for referral for lung transplantation has not been investigated yet.

In a large cohort of IPF patients, we aimed at describing the relationship between FVC and TLCO, both expressed as percentage of predicted values, focusing on the consequence of adopting either the “old” reference equations of the European Community for Steel and Coal (ECSC) or the new GLI equations. We also investigated whether or not adoption of the GLI equations modified the eligibility for lung transplantation in patients with IPF.

METHODS

COLIBRI-ILD cohort

COLIBRI-ILD, which is part of the COLIBRI program, was designed to provide specific standardized, structured, web-based medical consultations for interstitial lung disease (ILD) [18]. COLIBRI-ILD provides an unsupervised and unconstrained real-life database for observational research. All patients visiting a participating respiratory physician who had a

diagnosis of ILD could enter the database provided they gave oral consent after being informed by their physician. In 2020, the COLIBRI-ILD database comprised 146 voluntary respiratory physicians working in hospitals (78%) or private practices (22%) on the French metropolitan territory.

In accordance with French law, there was no requirement for written consent because the project was considered an observational cohort study. The database was authorized by the French national commission on personal data privacy (Commission Nationale de l'Informatique et des Libertés, CNIL, authorization number #2013–526). All entered data are stored in a secured central server certified for health data storage (OVH Healthcare, Claranet) [2]. The protocol was approved by the French Committee for Health Research Data Processing (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, CCTIRS, reference number #12.410.bis). The protocol was approved by the French ethical research committee (CPP reference number #2017 AO266251).

Patients

All patients included between January 2015 and December 2019 in the COLIBRI-ILD database with a diagnosis of IPF confirmed by a Multidisciplinary Diagnosis Discussion panel according to international guidelines [2,19] were considered for inclusion in the current analysis (Figure 1). Of note, patients diagnosed with combined pulmonary emphysema and fibrosis were not included. Collected data were gender, age, height and results of spirometry and TLCO measurements, these latter being performed at the same time. As predicted values are calculated based on age, gender and height, all patients for which at least one of these data were missing were excluded. As ethnic groups were not available for legal consideration, all patients were assumed to be Caucasian.

We retrieved only one dataset per patient. We first examined data collected at first medical follow-up (Baseline database). If a complete dataset was not available in this database, we then examined data collected during follow-up (Follow-up database). The first available complete dataset was retrieved in this base (Figure 1).

Statistical analyses

Values were expressed using either the references from the European Community for Steel and Coal (ECSC) [20,21] or those from the GLI [12,13].

All analyses were performed using the R statistical software, version 3.2.4. Results were considered statistically significant when the probability of a type I error was below 5%. Continuous data are presented as mean and standard deviations (SDs) while categorical data are presented as percentages.

RESULTS

Patients

Among the 417 patients with IPF included in the COLIBRI-ILD database, 215 had a complete dataset in the Baseline database and 33 who failed to have a complete dataset in the Baseline database had at least one complete dataset in the Follow-up database (Figure 1). Characteristics of the complete group (n=248) are presented in Table 1. When expressed as percentages of predicted values, mean FVC with the GLI equation was lower by 6% than with the ECSC equation ($P>0.05$); conversely, mean TLCO was higher (by 3%) with the GLI equation compared with the ECSC equation.

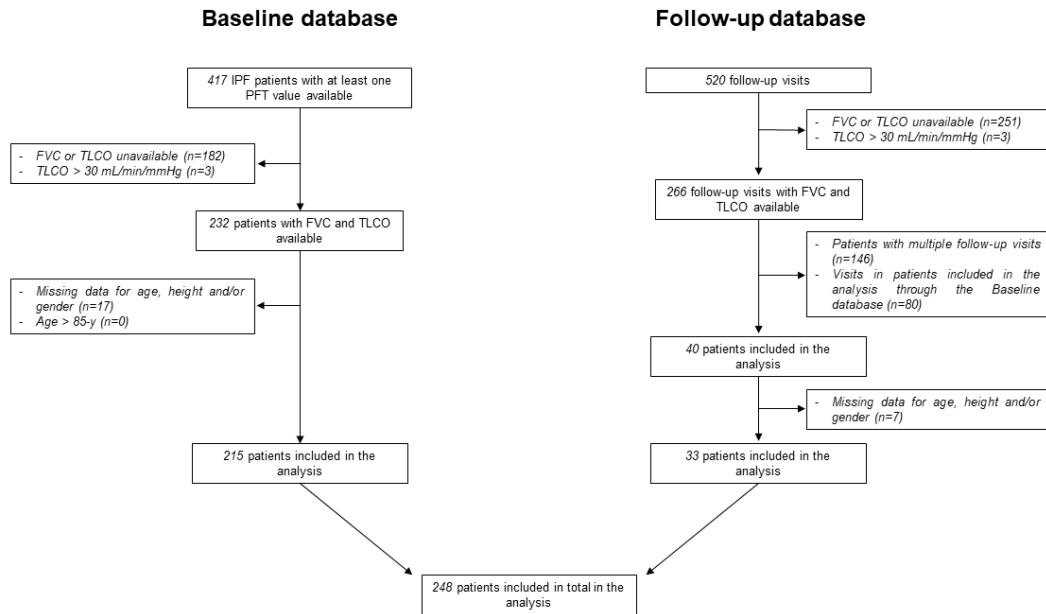


Figure 1. Flow chart. The initial database corresponds to the creation of patient files into COLIBRI-ILD with some data filled in by lung physicians. FVC and TL_{CO} can be entered at this point or later during the follow-up, once or more times. We kept one measurement of TL_{CO} and one measure of FVC per subject, entered at the same moment into the database, and technically performed at once (the first ones available).

Table 1. Characteristics of the 248 studied patients with IPF.

Variable	
Males, n (%)	190 (77%)
Age, years	72 ± 8
Height, cm	168 ± 9
FEV1, L	2.25 ± 0.66
FEV1, % pred ECSC	86 ± 21
FEV1, % pred GLI	83 ± 19
FVC, L	2.74 ± 0.85
FVC, % pred ECSC	83 ± 21
FVC, % pred GLI	77 ± 18
TLCO, mL/min/mmHg	12.28 ± 4.96
TLCO, % pred ECSC	52 ± 20
TLCO, % pred GLI	55 ± 21

FEV1: forced expiratory volume in 1s; ECSC: European Community for Steel and Coal; GLI: Global Lung function Initiative; FVC: forced vital capacity; TLCO: transfer of the lung for carbon monoxide.

Relationship between FVC and TLCO

The relationship between FVC and TLCO is displayed on Figure 2. Regardless of the equation used, the average value of FVC was above 80% of the predicted value as long as TLCO was above 50% of the predicted value (Figure 2A and 2B). In addition, mean FVC were similar whatever the TLCO as long as TLCO remained greater than 50% of the predicted value. By contrast, in patients with TLCO below 50% of the predicted value, mean FVC was below 80% of the predicted value and FVC, and the mean value of FVC decreased as the value of TLCO decreased.

When FVC and TLCO were expressed as z-scores with the GLI equations, FVC remained normal (i.e., z-score greater than -1.64) for TLCO values of z-scores as low as -3.50 (Figure 2C).

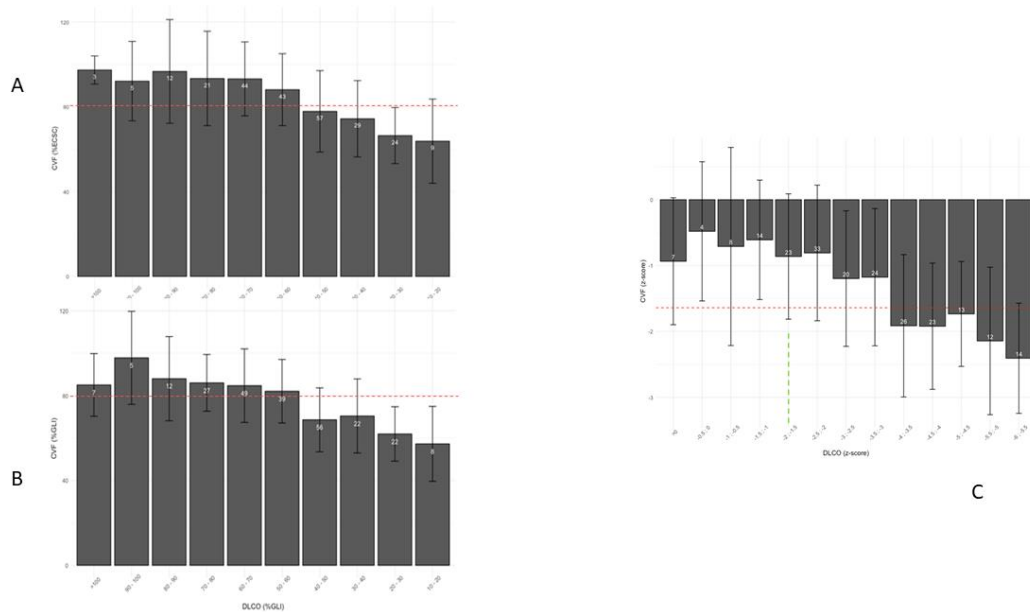


Figure 2. A and B: Transversal observation of the relationship between FVC and TLCO, expressed as a percentage of a reference value, using ECSC (A) and GLI (B). Per every 10% TLCO, we linked the mean value of FVC, expressed as a percentage of a reference value \pm 95 % confidence interval (black line). The white numbers represent the subjects per 10% TLCO. The dotted line indicates 80% of the predicted value for FVC.

C: Transversal observation of the relationship between FVC and TLCO, expressed as a Z-score. For each 0,5 SD of TLCO, we linked the mean values of FVC expressed as a Z-score \pm 95% confidence interval (black line). The horizontal dotted line indicates the LLN for FVC, equivalent to -1,64 Z-score, which means 5% of values are below this point. FVC remains normal on the left part of the graph. The vertical dotted line indicates the LLN for TLCO. The white numbers represent the subjects for each 0,5 SD of TLCO.

Potential impact of GLI equations on referral to lung transplantation

The Sankey diagram (Figure 3) displays the distribution of patients according to FVC (with a limit of 80% of predicted value) and to TLCO (with a limit of 40% of predicted value) in the two conditions (ECSC and GLI equations). All patients with $FVC \geq 80\%$ pred and $TLCO \geq 40\%$ pred with the GLI equations had also $FVC \geq 80\%$ pred and $TLCO \geq 40\%$ pred with the ECSC equations. By contrast, a subset of IPF patients with $FVC < 80\%$ pred and $TLCO \geq 40\%$ pred with the GLI equations had either $FVC \geq 80\%$ pred and $TLCO \geq 40\%$ pred (n=17), $FVC \geq 80\%$ pred and $TLCO < 40\%$ pred (n=2) or $FVC < 80\%$ pred and $TLCO < 40\%$ pred (n=8) with the ECSC equations. A large majority (96%) of patients with $FVC < 80\%$ pred and $TLCO < 40\%$ pred with the GLI equations had also $FVC < 80\%$ pred and $TLCO < 40\%$ pred with the ECSC equations.

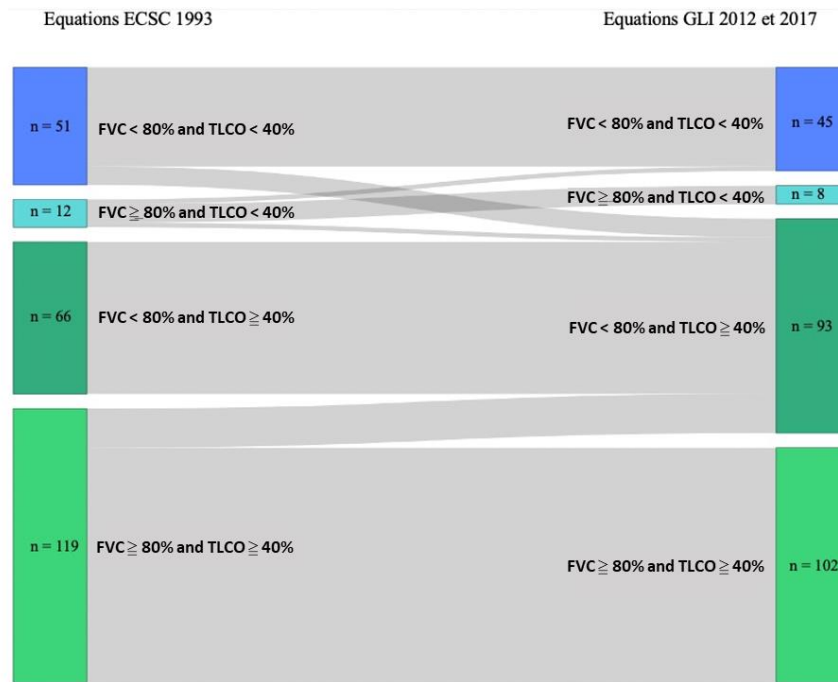


Figure 3. Sankey diagram. Classification of IPF patients according to FVC (either <80% or ≥80% of the predicted value) and to TLCO (either <40% or ≥40% of the predicted value) using either the ECSC or the GLI equations. Of note, the 2015 consensus for the selection of lung transplant candidates recommend to consider lung transplantation in IPF patients with FVC<80% or TLCO<40% of the predicted value. ECSC: European Community for Steel and Coal; GLI: Global Lung function Initiative; FVC: forced vital capacity; TLCO: transfer of the lung for carbon monoxide.

DISCUSSION

Although FVC and TLCO expressed as percentages of predicted values are widely used worldwide to monitor severity and progression of IPF, the relationship between these two parameters in IPF patients has not been formally studied. By analysing a real-life cohort of patients with IPF diagnosed according to approved criteria, we found the following: (i) there is no linear relationship between FVC and TLCO (expressed as percentages of predicted values) in patients with IPF, suggesting that these two parameters give different (and presumably complementary) information regarding consequences of IPF on pulmonary physiology; (ii) a majority of IPF patients with FVC either greater than 80% of predicted value (*i.e.*, those who are considered to have “normal” values) and/or with a z-score greater than -1.64 (a threshold corresponding to a statistically-defined lower limit of normal) had nevertheless an “abnormal” TLCO (*i.e.*, either <70% of predicted value and/or with a z-score < -1.64), suggesting that FVC is less sensitive than TLCO to quantify the lung involvement of IPF. In our study, these observations were made with the ECSC equations as well as with the new GLI equations. By comparison with ECSC equations, the use of the new GLI equations resulted in lower mean FVC value (% pred) and in higher mean TLCO value (% pred). As a consequence, the number of IPF patients who should be considered for lung transplantation (*i.e.*, those with FVC < 80% pred or TLCO < 40% pred) was higher (by 14%) with the GLI equations than with the ECSC equations.

The finding of a preserved FVC despite pulmonary restriction has already been reported in patients with IPF. In a cohort of 93 IPF patients, Cortes-Telles *et al.* have studied FVC as a function of restriction severity as assessed by total lung capacity (TLC) [22]. These authors found that although 73% of patients with IPF had a restrictive pattern during initial

evaluation, more than one-half (56%) had a normal FVC [22]. In addition, they reported that 40% of patients with restriction (based on a low TLC) had normal FVC, while none of the patients with low FVC had a normal TLC [22]. The pathophysiological mechanism should be the following. The excess production of extracellular matrix found in IPF changes the static mechanical properties of the lung, leading to a progressive increase in elastic recoil. The increase in elastic recoil in turn leads to a right-sided shift of the pressure/volume curve of the lungs, while the pressure/volume curve of the chest wall remains unchanged [6]. When the increase of lung elastic recoil is mild (*i.e.*, in the initial stages of IPF), TLC and residual volume (RV) decrease by a similar amount, and FVC remains normal [6]. It is only at the later stages, when lung fibrosis and elastic recoil worsen, that TLC decreases by a greater amount than RV and thus, FVC significantly decreases.

TLCO is the product of two separate but simultaneous measurements, the rate of uptake of CO from alveolar gas (KCO) and the alveolar volume (VA). In their study, Cortes-Telles *et al.* reported that “the average KCO ($\geq 86\%$ of predicted) remained within normal limits” despite most IPF patients had a restrictive pattern [22]. The interpretation of a “normal” KCO must be regarded cautiously in patients with a restrictive pattern. As clearly demonstrated by Glenet *et al.*, in patients with a restrictive pattern due to a chest abnormality (and with normal lungs), KCO increases when VA (and TLC) decreases [23]. The most likely explanation is an increased capillary blood volume with respect to the alveolar volume, leading to an increased rate of uptake of CO from alveolar gas. Thus, although “within normal limits”, a value of 86% of predicted value cannot be regarded as physiologically normal in IPF patients with a restrictive pattern. In our study, we were unfortunately unable to study the relationships between TLCO and VA and between TLCO and KCO because of too many missing data for VA and for KCO in the database.

According to the above physiological considerations, it could be considered surprising that FVC has been preferred to more sensitive measurements of lung function such as total lung capacity TLC and TLCO to measure of disease severity and progression in IPF. Reasons for that are multiple. First, spirometry is much more available than TLCO and TLC [24]. FVC can therefore be used to monitor IPF severity and progression not only in tertiary medical care (such as reference centers) but also in secondary and even in primary care settings (where spirometry can in some cases be available). Second, the cost of spirometry is much lower than the cost of TLCO and of TLC (less than on half in France). Third, the reproducibility and the repeatability of FVC is better than that of TLCO, mainly because of higher variability in TLCO than in FVC measurements between different devices [25].

Earlier diagnosis is considered to be a prerequisite for earlier treatment, and potentially for improvement of the long-term prognosis [26]. Our results strongly suggest that a preserved FVC in patients with IPF is not sufficient to exclude a yet severe pulmonary involvement (as quantified by TLCO). In other words, from the clinicians' perspective, our data support this idea that FVC can identify (and presumably quantify) an abnormally high lung elastic recoil only when the lung involvement of IPF is already severe [6]. Thus, a measurement of TLCO might be useful when IPF patients clinically deteriorate despite stable (and “normal”) FVC. In addition, our data suggest that selecting IPF patients eligible for antifibrotic drugs on the bases of FVC might be inappropriate. In some countries, antifibrotic drugs for IPF patients are only available to those with $FVC \leq 80\%$ of predicted value [16]. Our results suggest that this strategy is likely to miss patients with severe form of the disease.

Here, we analysed only transversal data. We are therefore unable to characterise the course of FVC and TLCO throughout disease progression in IPF patients. To do that, longitudinal data would have been necessary. However, to analyse longitudinal data is challenging because it

would necessitate a large number of measures per patient despite the frequency of late diagnosis and the short survival time. In addition, the high heterogeneity of disease progression between patients would make it difficult to interpret the simultaneous analysis of TLCO and FVC over time.

Our data show that using the GLI instead of the ECSC equations does not change the “shape” of the relationship between FVC and TLCO in IPF patients: a majority of IPF patients in our cohort had “normal” FVC values, and a large subset of them had nevertheless an “abnormal” TLCO. In addition, we confirm that adopting GLI equations to interpret pulmonary function tests in IPF would impact clinical decisions. As previously assessed, predicted values are higher for FVC and lower for TLCO using the GLI equations instead of the ECSC equations (and thus, the percentages of predicted values are lower for FVC and higher for TLCO) [11]. By examining the consideration for referral to lung transplantation only on the bases of FVC and TLCO (without considering neither age nor any clinical data), we found that the number of IPF patients who should be considered for lung transplantation was higher by 14% with the GLI equations than with the ECSC equations. The impact of such changes on patients’ survival warrants further studies.

There are several limitations in our study. First, among the included patients (who had by definition a TLCO result that was available in the database), only a minority had also available values for KCO and VA. We are therefore unable to determine whether the decreases in TLCO were driven by decreases in VA (*i.e.*, by the restrictive pattern of IPF) or by decreases in KCO (*i.e.*, by the consequences of IPF on the alveolar-capillary function). Second, we used an unsupervised and unconstrained real-life database. This can be regarded both a strength and as a weakness. The advantage to use a real-life database is that patients, who had all a diagnosis of IPF confirmed by a multidisciplinary diagnosis discussion panel

made according to international guidelines, were not selected on any basis. This is in contrast with many studies conducted in IPF patients, who comprised highly selected groups of patients included in therapeutic trials [3,27]. Our results are therefore likely to be applicable to most IPF patients. The unsupervised, unconstrained and unmonitored feature our database can however be regarded as a weakness. Indeed, performing pulmonary function tests according to high standard recommendations can be challenging, especially for measurements of TLCO. We therefore cannot exclude some uncontrolled measurement bias that might have influenced our results.

In conclusion, our analyses highlight and clarify the lack of robustness of FVC to stratify IPF severity in about half a real-life large cohort of unselected patients. Although FVC has been shown to be a valuable parameter to quantify severity and to monitor disease progression in IPF patients with the most severe forms (*i.e.*, those with TLCO less than ~45-50% of predicted value), this parameter lacks sensitivity in patients with less severe forms. As earlier treatments are thought to improve prognosis, this suggests that identifying patients eligible for antifibrotic drugs on the bases of FVC is inappropriate. Our analyses also confirm that using the new GLI equations may change medical decisions, including referral to lung transplantation.

CONCLUSION

THÈSE SOUTENUE PAR : Salomé NUSSBAUM

TITRE : CAPACITE VITALE FORCEE ET DIFFUSION DU MONOXYDE DE CARBONE DANS LA FIBROSE PULMONAIRE IDIOPATHIQUE : CE QUE CHANGE L'UTILISATION DES NORMES GLI

CONCLUSION :

Cette observation transversale de 248 patients porteurs d'une fibrose pulmonaire idiopathique (FPI) nous a permis de décrire la relation non linéaire entre la capacité vitale forcée (CVF) et la diffusion du monoxyde de carbone (DL_{CO}), les deux paramètres fonctionnels indispensables à l'évaluation et au suivi de la maladie. La cohorte française COLIBRI-PID dont ils sont issus rassemble des données de vraie vie, avec des formes de gravité très hétérogène, et un diagnostic consensuel. Ces résultats pourraient caractériser l'évolution de la CVF et de la DL_{CO} à travers le temps pour un patient donné lorsque la fibrose progresse : une première phase de la maladie marquée par un déclin de la DL_{CO} , mais une CVF stable au-dessus de 80 % de la valeur prédite et au-dessus de la limite inférieure de la norme (LIN), et une phase plus tardive où CVF et DL_{CO} chuteraient ensemble. Cette hypothèse devra être confirmée par des études longitudinales. L'utilisation des normes GLI et ECSC retrouve des aspects semblables, avec une cassure survenant pour une DL_{CO} entre 40 % et 50 %, et une CVF autour de 75 %. La conférence de consensus de 2015 recommande d'adresser le patient à un centre de transplantation pulmonaire lorsque la CVF est inférieure à 80 % ou lorsque la DL_{CO} est inférieure à 40 %. Un petit nombre de patients sont éligibles à la greffe plus précocement lorsque l'on utilise GLI au lieu de ECSC. Comme dans la population générale après 40 ans, l'utilisation de la LIN est moins sensible que la limite de 80 % de la valeur prédite pour détecter une CVF basse. En effet, la dispersion des valeurs autour de la moyenne s'amplifie avec l'âge dans la population de référence, ainsi la LIN est inférieure à 80 % de la valeur prédite chez ces patients porteurs de FPI en raison de leur âge. La DL_{CO} s'avère la plus sensible pour évaluer les formes de FPI à capacité vitale préservée. Son utilisation à bon escient pourrait favoriser un diagnostic et une prise en charge plus précoce lorsque le tableau clinique est faussement rassurant et les volumes mobilisables normaux. L'utilisation de la LIN selon GLI détecte une CVF basse pour une minorité de formes de FPI, probablement les plus sévères.

VU ET PERMIS D'IMPRIMER
Grenoble, le 17-07-2021

LE DOYEN



Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE

Pr. Christophe PISON

REFERENCES

- [1] E.R. Parra, R.A. Kairalla, C.R.R. de Carvalho, V.L. Capelozzi, Abnormal deposition of collagen/elastic vascular fibres and prognostic significance in idiopathic interstitial pneumonias, *Thorax*. 62 (2007) 428–437. <https://doi.org/10.1136/thx.2006.062687>.
- [2] G. Raghu, M. Remy-Jardin, J.L. Myers, L. Richeldi, C.J. Ryerson, D.J. Lederer, J. Behr, V. Cottin, S.K. Danoff, F. Morell, K.R. Flaherty, A. Wells, F.J. Martinez, A. Azuma, T.J. Bice, D. Bouros, K.K. Brown, H.R. Collard, A. Duggal, L. Galvin, Y. Inoue, R.G. Jenkins, T. Johkoh, E.A. Kazerooni, M. Kitaichi, S.L. Knight, G. Mansour, A.G. Nicholson, S.N.J. Pipavath, I. Buendía-Roldán, M. Selman, W.D. Travis, S. Walsh, K.C. Wilson, American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society, Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline, *Am J Respir Crit Care Med*. 198 (2018) e44–e68. <https://doi.org/10.1164/rccm.201807-1255ST>.
- [3] A.U. Wells, S.R. Desai, M.B. Rubens, N.S.L. Goh, D. Cramer, A.G. Nicholson, T.V. Colby, R.M. du Bois, D.M. Hansell, Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed by computed tomography, *Am J Respir Crit Care Med*. 167 (2003) 962–969. <https://doi.org/10.1164/rccm.2111053>.
- [4] J. Behr, Disease Progression in Idiopathic Pulmonary Fibrosis. FVC Is Not Enough, *Am J Respir Crit Care Med*. 196 (2017) 1094–1095. <https://doi.org/10.1164/rccm.201706-1246ED>.
- [5] A. Cortes-Telles, L. Forkert, D.E. O'Donnell, O. Moran-Mendoza, Idiopathic pulmonary fibrosis: new insights on functional characteristics at diagnosis, *Can Respir J*. 21 (2014) e55-60. <https://doi.org/10.1155/2014/825606>.

- [6] B. Degano, T. Soumagne, G. Eberst, N. Méaux-Ruault, H. Gil, N. Magy-Bertrand, Pulmonary Function Parameters Other Than Vital Capacity Should Be Considered in Screening for Interstitial Lung Disease in Patients With Systemic Sclerosis: Comment on the Article by Suliman et al, *Arthritis Rheumatol.* 68 (2016) 2346–2347. <https://doi.org/10.1002/art.39778>.
- [7] S.D. Nathan, K.C. Meyer, IPF clinical trial design and endpoints, *Curr Opin Pulm Med.* 20 (2014) 463–471. <https://doi.org/10.1097/MCP.0000000000000091>.
- [8] B. Ley, H.R. Collard, T.E. King, Clinical course and prediction of survival in idiopathic pulmonary fibrosis, *Am J Respir Crit Care Med.* 183 (2011) 431–440. <https://doi.org/10.1164/rccm.201006-0894CI>.
- [9] R.M. Cherniack, T.V. Colby, A. Flint, W.M. Thurlbeck, J.A. Waldron, L. Ackerson, M.I. Schwarz, T.E. King, Correlation of structure and function in idiopathic pulmonary fibrosis, *Am J Respir Crit Care Med.* 151 (1995) 1180–1188. <https://doi.org/10.1164/ajrccm/151.4.1180>.
- [10] C. Sharp, H.I. Adamali, A.B. Millar, A comparison of published multidimensional indices to predict outcome in idiopathic pulmonary fibrosis, *ERJ Open Res.* 3 (2017) 00096–02016. <https://doi.org/10.1183/23120541.00096-2016>.
- [11] T. Soumagne, A. Guillien, A. Chambellan, T. Hua-Huy, A.T. Dinh-Xuan, B. Degano, Global Lung Initiative equations for pulmonary hypertension screening in systemic sclerosis, *Eur Respir J.* 52 (2018) 1800528. <https://doi.org/10.1183/13993003.00528-2018>.
- [12] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, P.L. Enright, J.L. Hankinson, M.S.M. Ip, J. Zheng, J. Stocks, ERS Global Lung Function Initiative, Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, *Eur Respir J.* 40 (2012) 1324–1343.

<https://doi.org/10.1183/09031936.00080312>.

[13] S. Stanojevic, B.L. Graham, B.G. Cooper, B.R. Thompson, K.W. Carter, R.W. Francis, G.L. Hall, Global Lung Function Initiative TLCO working group, Global Lung Function Initiative (GLI) TLCO, Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians, *Eur Respir J*. 50 (2017) 1700010. <https://doi.org/10.1183/13993003.00010-2017>.

[14] S. Stanojevic, Standardisation of lung function test interpretation: Global Lung Function Initiative, *Lancet Respir Med*. 6 (2018) 10–12. [https://doi.org/10.1016/S2213-2600\(17\)30472-1](https://doi.org/10.1016/S2213-2600(17)30472-1).

[15] A. Burgess, K. Goon, J.D. Brannan, J. Attia, K. Palazzi, C. Oldmeadow, T.J. Corte, I. Gaspole, N. Goh, G. Keir, H. Allan, S. Chapman, W. Cooper, S. Ellis, P. Hopkins, Y. Moodley, P. Reynolds, C. Zappala, S. Macansh, C. Grainge, Eligibility for anti-fibrotic treatment in idiopathic pulmonary fibrosis depends on the predictive equation used for pulmonary function testing, *Respirology*. 24 (2019) 988–995. <https://doi.org/10.1111/resp.13540>.

[16] K. Ward, L. Spurr, N.R. Goldman, G.A. Margaritopoulos, M. Kokosi, E. Renzoni, F. Chua, T.M. Maher, S. Ward, A.U. Wells, Patient eligibility for anti-fibrotic therapy in idiopathic pulmonary fibrosis can be altered by use of different sets of reference values for calculation of FVC percent predicted, *Respiratory Medicine*. 120 (2016) 131–133. <https://doi.org/10.1016/j.rmed.2016.10.007>.

[17] D. Weill, C. Benden, P.A. Corris, J.H. Dark, R.D. Davis, S. Keshavjee, D.J. Lederer, M.J. Mulligan, G.A. Patterson, L.G. Singer, G.I. Snell, G.M. Verleden, M.R. Zamora, A.R. Glanville, A consensus document for the selection of lung transplant candidates: 2014--an update from the Pulmonary Transplantation Council of the International Society for Heart and

Lung Transplantation, *J Heart Lung Transplant.* 34 (2015) 1–15.
<https://doi.org/10.1016/j.healun.2014.06.014>.

[18] E. Kelkel, F. Herengt, H. Ben Saidane, D. Veale, C. Jeanjean, C. Pison, J. Pernot, J.-L. Pépin, B. Guillaud-Segard, J. Gonzalez-Bermejo, B. Aguilaniu, [COLIBRI: Improving clinical practice and producing relevant scientific data], *Rev Mal Respir.* 33 (2016) 5–16.
<https://doi.org/10.1016/j.rmr.2015.02.090>.

[19] G. Raghu, H.R. Collard, J.J. Egan, F.J. Martinez, J. Behr, K.K. Brown, T.V. Colby, J.-F. Cordier, K.R. Flaherty, J.A. Lasky, D.A. Lynch, J.H. Ryu, J.J. Swigris, A.U. Wells, J. Ancochea, D. Bouros, C. Carvalho, U. Costabel, M. Ebina, D.M. Hansell, T. Johkoh, D.S. Kim, T.E. King, Y. Kondoh, J. Myers, N.L. Müller, A.G. Nicholson, L. Richeldi, M. Selman, R.F. Dudden, B.S. Griss, S.L. Protzko, H.J. Schünemann, ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis, An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, *Am J Respir Crit Care Med.* 183 (2011) 788–824. <https://doi.org/10.1164/rccm.2009-040GL>.

[20] R.O. Crapo, A.H. Morris, Standardized single breath normal values for carbon monoxide diffusing capacity, *Am Rev Respir Dis.* 123 (1981) 185–189.
<https://doi.org/10.1164/arrd.1981.123.2.185>.

[21] P.H. Quanjer, G.J. Tammeling, J.E. Cotes, O.F. Pedersen, R. Peslin, J.C. Yernault, Lung volumes and forced ventilatory flows, *Eur Respir J.* 6 Suppl 16 (1993) 5–40.
<https://doi.org/10.1183/09041950.005s1693>.

[22] A. Cortes-Telles, L. Forkert, D.E. O’Donnell, O. Moran-Mendoza, Idiopathic pulmonary fibrosis: new insights on functional characteristics at diagnosis, *Can Respir J.* 21 (2014) e55-60. <https://doi.org/10.1155/2014/825606>.

[23] S.N. Glénet, C. De Bisschop, F. Vargas, H.J.P. Guénard, Deciphering the nitric oxide

to carbon monoxide lung transfer ratio: physiological implications, *J Physiol.* 582 (2007) 767–775. <https://doi.org/10.1113/jphysiol.2007.133405>.

[24] P. Enright Md, Office-based DLCO tests help pulmonologists to make important clinical decisions, *Respir Investig.* 54 (2016) 305–311. <https://doi.org/10.1016/j.resinv.2016.03.006>.

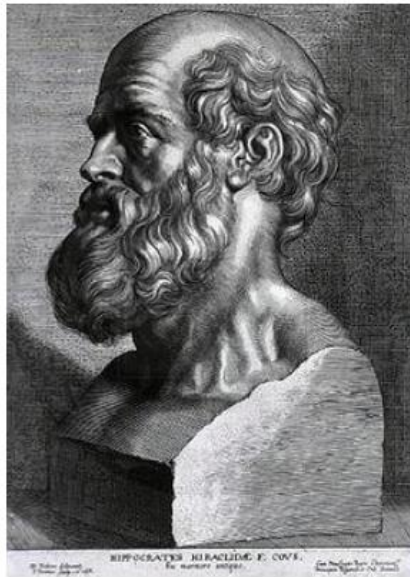
[25] R.L. Jensen, J.G. Teeter, R.D. England, H.M. Howell, H.J. White, E.H. Pickering, R.O. Crapo, Sources of long-term variability in measurements of lung function: implications for interpretation and clinical trial design, *Chest.* 132 (2007) 396–402. <https://doi.org/10.1378/chest.06-1999>.

[26] V. Cottin, L. Richeldi, Neglected evidence in idiopathic pulmonary fibrosis and the importance of early diagnosis and treatment, *Eur Respir Rev.* 23 (2014) 106–110. <https://doi.org/10.1183/09059180.00008613>.

[27] B. Ley, W.Z. Bradford, D. Weycker, E. Vittinghoff, R.M. du Bois, H.R. Collard, Unified baseline and longitudinal mortality prediction in idiopathic pulmonary fibrosis, *Eur Respir J.* 45 (2015) 1374–1381. <https://doi.org/10.1183/09031936.00146314>.

Remerciements

À Alicia pour son aide précieuse, à Bruno Degano pour ses idées, à ceux qui ont créé et complété la base de données COLIBRI, et aux membres du jury.



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

CAPACITE VITALE FORCEE ET DIFFUSION DU MONOXYDE DE CARBONE DANS LA FIBROSE PULMONAIRE IDIOPATHIQUE : CE QUE CHANGE L'UTILISATION DES NORMES GLI

RÉSUMÉ :

Contexte : CVF et DLCO sont les paramètres physiologiques les plus utilisés pour l'évaluation des patients porteurs d'une fibrose pulmonaire idiopathique (FPI). Ils sont exprimés en pourcentage d'une valeur de référence ou en Z-score, et l'utilisation des équations du Global Lung Initiative (GLI) est recommandée depuis peu. Les objectifs étaient de décrire la relation entre CVF et DLCO, et d'évaluer l'influence du changement des valeurs de référence sur la décision médicale, notamment concernant la sélection des candidats à la transplantation pulmonaire.

Méthode : nous avons inclus tous les sujets de la cohorte COLIBRI-PID porteurs d'une FPI. Pour chacun, une mesure de DLCO et une mesure de CVF ont été recueillies.

Résultats : cette observation transversale de 248 patients avec un large éventail de sévérité, a permis de montrer la relation non linéaire entre CVF et DLCO. Ces résultats sont susceptibles de caractériser l'évolution de la CVF et de la DLCO lorsque la maladie progresse, pour un patient donné : on pourrait alors identifier une première phase de déclin de la DLCO avec une CVF plutôt stable, puis une phase plus tardive où ces deux paramètres chutent ensemble. 17 patients ont changé de groupe pour être adressés vers un centre de transplantation pulmonaire en utilisant les équations GLI à la place des anciennes normes. Les valeurs limites considérées par le consensus de transplantation pulmonaire étaient de 40 % pour la DLCO ou 80 % pour la CVF.

Conclusion : La DLCO semble essentielle à l'évaluation des formes de FPI à CVF préservée. L'utilisation de GLI est un plus sensible que les normes plus anciennes pour sélectionner les candidats à la transplantation pulmonaire.

ABSTRACT :

Title : Insight into the relationship between forced vital capacity and transfer factor of the lung for carbon monoxide in patients with idiopathic pulmonary fibrosis.

Background : FVC and DLCO are the most useful physiological parameters to assess idiopathic pulmonary fibrosis (IPF). They are expressed as percentage of reference value or Z-score, and the use of Global Lung Initiative (GLI) equations is now recommended. The objectives were to describe the relationship between FVC and DLCO, and to assess the influence of the change in reference values on medical decision, namely regarding the selection of lung transplant candidates.

Methods : we included all subjects diagnosed with IPF from the cohort COLIBRI-ILD. Measurements of FVC and DLCO performed at the same time were collected for each patient.

Results : in 248 IPF patients with a broad range of severity, this transversal observation highlighted the nonlinear relationship between FVC and DLCO. Those results could allow us to characterise the course of FVC and DLCO throughout disease progression for a given patient. In the first stages, FVC would remain steady while DLCO would drop. In contrast, both would decline in the last stages. 17 patients switch group to be referred to a lung transplant center when we use GLI instead of the older standards, with the cut-off limit of 40 % for DLCO or 80 % for FVC.

Conclusion : DLCO seems essential in monitoring the IPF forms when FVC is preserved. The use of GLI is little more sensitive than older standards to select lung transplant candidates.

MOTS CLÉS : Fibrose pulmonaire idiopathique, capacité vitale forcée, diffusion du monoxyde de carbone, normes GLI

SPÉCIALITÉ : Pneumologie