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Impact of Lung Biopsy on Lung Function in Idiopathic Pulmonary Fibrosis

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Keywords
Biopsy · Exacerbation · Interstitial lung disease · Lung function · Surgery

Abstract
Background: Video-assisted surgical lung biopsy (SLB) is performed in 10–30% of cases to establish the diagnosis of idiopathic pulmonary fibrosis (IPF). ***Objectives:*** The aim of the study was to analyze the impact of SLB on lung function in patients eventually diagnosed with IPF. ***Methods:*** This is an observational, retrospective, monocentric study of all consecutive patients eventually diagnosed with IPF in multidisciplinary discussion who underwent SLB over 10 years in a specialized center. The primary end point was the variation in forced vital capacity (FVC) before and after the SLB. The secondary end points were the variations in forced expiratory volume in one second (FEV1), total lung capacity (TLC), carbon monoxide diffusion capacity (DLCO), and morbidity and mortality associated with the SLB. ***Results:*** In 118 patients who underwent SLB and were diagnosed with IPF, a relative decrease in FVC of 4.8% ($p < 0.001$) was found between measurements performed before and after the procedure. The mean FVC decrease was 156 ± 386 mL in an average period of 185 days, representing an annualized decline of 363 ± 764 mL/year. A significant decrease was also observed after SLB in FEV1, TLC, and DLCO. Complications within 30 days of SLB occurred in 14.4% of patients. Two patients (1.7%) died within 30 days, where one of them had poor lung function. Survival at 1 year was significantly poorer in patients with FVC <50% at baseline. ***Conclusion:*** In this uncontrolled study in patients ultimately diagnosed with IPF, SLB was followed by a significant decline in FVC, which appears to be numerically greater than the average decline in the absence of treatment in the literature. ***Summary at a Glance:*** This study evaluated the change in lung function in 118 consecutive patients diagnosed with idiopathic pulmonary fibrosis by surgical lung biopsy. Forced vital capacity decreased by 156 ± 386 mL in a mean of 185 days between the last measurement before and first measurement after biopsy, representing an annualized decline of 363 ± 764 mL/year.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a rare and severe chronic lung disease, with a median survival rate of <2–5 years without treatment [1, 2]. The disease course is characterized by a progressive restrictive ventilatory defect with a decline in FVC and total lung capacity (TLC), with interindividual and intraindividual variability [2]. FVC decreases on average by 0.13–0.21 L per year [3]. Decline in FVC, TLC, forced expiratory volume in one second (FEV1), and carbon monoxide diffusion capacity (DLCO) over the first 6–12 months following diagnosis of IPF are predictive factors for mortality [4]. A decrease in FVC of 10% or more within 6 months after diagnosis is an independent risk factor for mortality, with a better predictive value than alteration of DLCO [5]. The estimated minimal clinical difference in FVC is 2–6% and is correlated with a deterioration in quality of life [6] and worse prognosis [7]. Furthermore, FVC is the primary end point used in most therapeutic trials [8].

According to international guidelines, IPF is defined as a specific form of chronic progressive fibrosing interstitial pneumonia of unknown cause, occurring in older adults, confined to the lung, and associated with a histological and/or radiological pattern of usual interstitial pneumonia (UIP) [9, 10]. In about one-third of cases, clinical and radiological criteria are not sufficient to ascertain the diagnosis, and surgical lung biopsy (SLB) is contemplated [9], depending on the clinical context [11]. The most commonly used method of SLB is video-assisted thoracoscopic surgery (VATS), which is associated with less morbidity [12] and reduced operative time and hospital stay as compared to open lung surgery [13, 14]. Transbronchial cryobiopsy may also contribute to the diagnosis of IPF similar to VATS biopsy, with less morbidity and a lower risk of mortality [15]; however, the technique is not broadly available.

Currently, particular attention is being paid to assessing the risk and morbidity of SLB, which need be balanced with the benefit of making or securing a diagnosis of IPF [16]. Using hospital statistics from a national secondary care data set in the UK from 1997 to 2008, Hutchinson et al. [17] estimated in-hospital mortality following SLB to be 1.7%, the 30-day mortality to be 2.4%, and the 90-day mortality to be 3.9%. Practice has changed since that period and it is conceivable that mortality may now be lower, with the use of VATS and a better knowledge of risk factors. However, despite better knowledge of morbidity and short-term mortality associated with VATS-SLB, its potential impact on lung function is unknown. Furthermore, most studies evaluated the risk of SLB in interstitial lung disease in general, whereas a greater risk may exist in individuals with IPF as compared to non-IPF interstitial lung diseases.

The objective of this study was to evaluate the evolution of FVC after VATS-SLB in patients eventually diagnosed with IPF, with the hypothesis that SLB would be associated with significant decline in lung function. The secondary objectives were to evaluate the change in other lung function parameters and to assess the morbidity and mortality of SLB.

Material and Methods

Patients

This observational, retrospective, monocentric study was carried out in a tertiary university hospital. All consecutive patients who underwent SLB in the thoracic surgery department over 10 years (March 2007 to March 2017) and whose pathological diagnosis was "pulmonary fibrosis" were selected using files from the pathology department. Data collection ended on October 15, 2017. Data from all patients whose final diagnosis after multidisciplinary discussion was IPF were analyzed. Cases of IPF combined with emphysema (>15% extent of emphysema at CT), and familial or genetic cases of IPF, were not excluded. Patients whose diagnosis was obtained by segmentectomy, lobectomy, or pneumonectomy were excluded.

Data Collection

Data were collected from the electronic patients' records. Pulmonary function test (PFT) data were collected, selecting the closest measurements prior to and following the VATS biopsy. PFTs following surgery were performed when patients could perform spirometry without pain. We also registered complications occurring within 1 month of the biopsy and of severe events (death and/or acute exacerbations) within 1 year of the biopsy.

This study was conducted under Reference Methodology MR004 [18] and was approved by the National Commission for Information Technology and Liberties of the Hospices Civils de Lyon (#17-251). In accordance with French legislation and the Hospices Civils de Lyon Research Ethics Committee, patients received a written information about the use of their data and their unrestricted right to remove them from the database.

Statistical Analysis

The primary end point was the relative decline in FVC (ΔFVC) from the last measurement performed before the biopsy to the first measurement performed after the biopsy. The relative change in FVC was calculated by the formula $({}_{\text{pre-biopsy}}\text{FVC} - {}_{\text{post-biopsy}}\text{FVC})/{}_{\text{pre-biopsy}}\text{FVC}$, using FVC in liters or percent predicted. For example, a patient whose FVC would decrease from 54% of predicted value prior to the biopsy to 46% following the biopsy will have a relative FVC decrease of $(54–46)/54 \times 100 = 14.8\%$. Secondary end points were relative changes in FEV1, TLC, DLCO, and complications in the month and year following the biopsy.

Table 1. Population characteristics

Total population, *n* (%)	118 (100)
Age, mean ± SD, years[a]	66±7
Gender, *n* (%)	
Male	91 (77)
Female	27 (23)
Smoking status, *n* (%)	
Active smoker	4 (3.4)
Former smoker	71 (60.2)
Never smoker	43 (36.4)
BMI, kg m^{-2}[a]	28±4.5

[a] Values are shown as median with maximum and minimum values or mean ± standard deviation.

To describe the population, we used percentages for qualitative variables and means ± SD or medians for quantitative variables. The assumption of a normal distribution of the quantitative variables was evaluated by the Kolmogorov-Smirnov test and graphically checked with a histogram. Continuous variables were compared using the Student *t* test or a Mann-Whitney test. Qualitative variables were compared using the χ^2 test or Fisher's exact test. For survival analyzes, the Kaplan-Meier method was used to estimate survival medians with a 95% confidence interval (CI). We used the Cox model for hazard ratio calculations for comparisons between different groups with 95% CI. A logistic regression analysis was used to estimate the odds ratio with a 95% CI between the different groups compared. Results were considered significant for *p* value <0.05. All analyses were performed using a statistical software package IBM SPSS for Windows, version 20.0 (IBM SPSS Inc., Chicago, IL, USA).

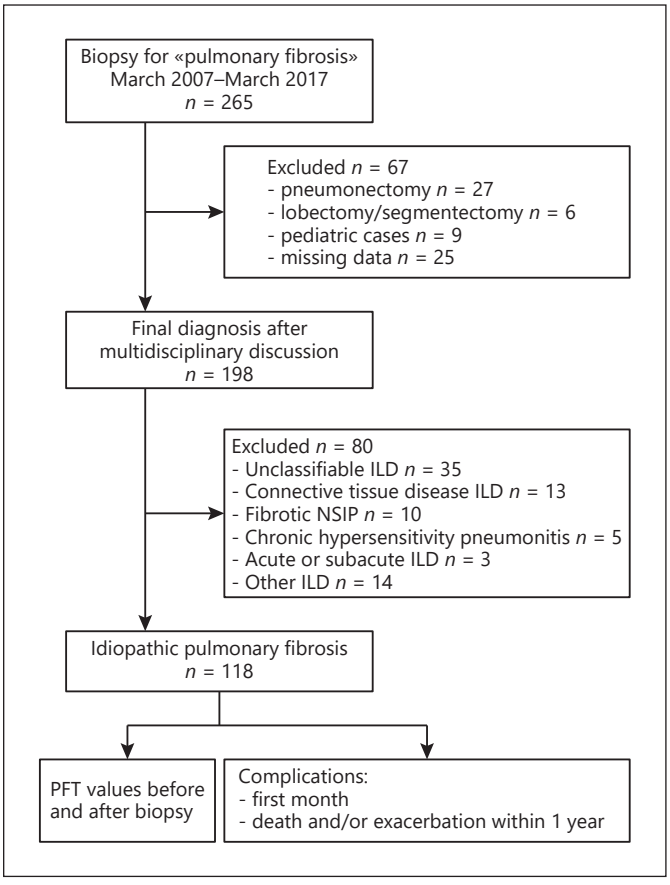

Fig. 1. Flow chart. IPF, idiopathic pulmonary fibrosis; PFT, pulmonary function test.

Results

Study Population and Patients' Characteristics

Of all SLBs performed during the study period, 265 patients had a histological diagnosis comprising "pulmonary fibrosis"; 67 were excluded due to the type of surgery or missing data, 80 were excluded due to a diagnosis other than IPF (Fig. 1), and 118 patients with IPF were included into the analysis. The biopsy was performed using VATS in 117 cases, and VATS converted into OLB in 1 case. The demographic characteristics are summarized in Table 1. The mean age at the time of the biopsy was 66 ± 7 years, with 46 patients (39%) older than 70 years and 16 patients (13.6%) older than 75 years.

Lung function parameters before the lung biopsy are shown in Table 2. Lung volumes were relatively preserved at diagnosis, with a mean FVC of 78% of predicted value. The mean DLCO was 53% of predicted value.

Relative Change in FVC (Primary End point)

FVC significantly decreased from a mean of 78.1% of predicted value at the last measurement before the biopsy to a mean of 74.9% of predicted value at the first measurement after the biopsy, representing a relative decrease of 4.8% (Table 2). The mean absolute decrease in FVC was 156 ± 386 mL, corresponding to a mean annualized decrease of 363 ± 764 mL/year. Compared to the pre-biopsy spirometry, 34 patients (28.8%) had a relative decrease in FVC ≥10% at the time of the first spirometry following the lung biopsy, 21 (17.8%) had a decrease in FVC of 5–10%, and 53 patients (44.9%) had a decrease in FVC <5% (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000509557). In univariate analysis, there was no correlation between baseline parameters (age, sex, smoking status, BMI, and FVC) and FVC change.

Table 2. Comparison of PFT between the last PFT before SLB and first PFT after the SLB

	Preoperative PFT	Postoperative PFT	Relative variation, %	Absolute variation, L	*p* value
FVC, % pred	78.1±16.9	74.9±19.1	−4.8		<0.001
FVC, L	2.79±0.87	2.69±0.88		−0.156±0.386	<0.001
FEV1, % pred	81.7±18.2	78.2±19.3	−5.4		<0.001
FEV1, L	2.23±0.68	2.14±0.68		−0.138±0.312	<0.001
TLC, % pred	71.8±14.8	67.4±15.8	−6.1		<0.001
TLC, L	4.42±1.2	4.17±1.2		−0.282±0.616	<0.001
DLCO, % pred	53±16	48±17	−4.5		<0.001
Median PFT delay			185 days [61–691]		

PFT, pulmonary function test; SLB, surgical lung biopsy; FVC, forced vital capacity; TLC, total lung capacity; FEV1, forced expiratory volume in one second.

Table 3. Early postoperative complications (within 30 days of surgery)

	N (%)
Type of complications	
Cardiogenic pulmonary edema	3 (2.5)
Infectious pneumonia	3 (2.5)
Lung collapse	1 (0.8)
Persistent air leak	1 (0.8)
Pleural effusion	1 (0.8)
Conversion to open lung surgery	1 (0.8)
Acute exacerbation of IPF	1 (0.8)
Death within 30 days[a]	2 (1.7)
Other	5 (4.2)
Total complications	17 (14.4)

IPF, idiopathic pulmonary fibrosis. [a] Death related to acute exacerbation of IPF (1 case) and sudden death of unknown origin (1 case).

Other Pulmonary Function Tests

Comparing the last measurement performed before the biopsy to the first measurement after the biopsy, a statistically significant decline was found in TLC (relative decrease of 6.1%), FEV1 (relative decrease of 5.4%), and DLCO (relative decrease of 4.5%) (Table 2). No correlation was found between baseline parameters (age, sex, smoking status, BMI, and FVC) and change in TLC, FEV1, or DLCO.

Morbidity and Mortality

Postsurgical complications in the month following SLB occurred in 17 cases (14.4%). The most frequent complications were cardiogenic pulmonary edema (3 patients, 2.5%) and infectious pneumonia (3 patients, 2.5%). Other early complications were lung collapse, persistent air leak, and pleural effusion (Table 3). Two patients (1.7%) died in the first month following the biopsy, 1 from a sudden death of unknown origin (FVC was 71%, and DLCO was 62% prior to the biopsy), and 1 from acute exacerbation of IPF (biopsy was performed during accelerated course, and FVC was already <50%).

Eight patients (6.8%) had an acute exacerbation of IPF within the first year following the SLB. The rate of IPF exacerbation at 1 year was significantly related to baseline FVC, with rates of 0, 16.7, 0, and 33.3% respectively, in categories of baseline FVC of >75, 60–75, 50–60, and <50%, respectively (Fisher's exact test, $p = 0.001$) (Table 4).

A total of 10 patients (8.5%) died (from all causes) within 1 year following the SLB. As expected, the 1-year survival and the overall survival were significantly lower in patients with low baseline FVC (Table 4; Fig. 2; online suppl. Tables 2, 3). In univariate analysis, baseline DLCO was not significantly associated with the occurrence of postsurgical complications, IPF exacerbations, or mortality.

Discussion

SLB was associated with a decrease in mean FVC from 78.1 to 74.9% of predictive value, representing a relative mean decrease of 4.8%, a mean absolute decrease of 156 ± 386 mL, and a mean annualized decrease of 363 ± 764 mL/year. Such change in FVC is clinically significant [4, 6] and is greater than the minimal clinically significant difference [6]. It is also greater than the average decline in FVC in the placebo arms of therapeutic trials in IPF

Table 4. Complications according to initial characteristics

	Patients *n* (%)	Complications at 1 month, *n* (%)	IPF exacerbation at 1 year, *n* (%)	Death at 1 year, *n* (%)
FVC before biopsy				
FVC ≥75%	69 (58.5)	9 (13)	0 (0)	1 (1.4)
FVC 60–74%	36 (30.5)	5 (14)	6 (16.7)	6 (16.7)
FVC 50–59%	4 (3.4)	0 (0)	0 (0)	0 (0)
FVC <50%	6 (5.1)	2 (33.3)	2 (33.3)	3 (50)
Missing data	3 (2.5)			
		$p = 0.47$	$p = 0.001$	$p = 0.001$
DLCO before biopsy				
DLCO ≥60%	24 (20.3)	2 (8.3)	0 (0)	1 (4.2)
DLCO 40–60%	51 (43.2)	11 (21.6)	3 (5.9)	5 (9.8)
DLCO <40%	14 (11.9)	2 (14.3)	1 (7.1)	0 (0)
Missing data	29 (24.6)			
		$p = 0.97$	$p = 0.36$	$p = 0.44$

Percentages in column "patients" refer to the proportion of patients in each category of FVC. Percentages in further columns refer to the proportion of patients within each category of FVC who had the corresponding complications. IPF, idiopathic pulmonary fibrosis; FVC, forced vital capacity; DLCO, carbon monoxide diffusion capacity.

(0.13–0.21 L per year) [3, 8, 19, 20]. Analysis by categories of FVC decline also suggested possible greater disease progression as compared to published cohorts of IPF patients not receiving antifibrotic therapy, who had a stable FVC (FVC decrease <5%) in 49–51% of patients, a marginal 5–10% decline in FVC in 20–23% of patients, and a decline ≥10% in 26–30% of patients, 6 months after the diagnosis of IPF [21, 22].

The results of this retrospective study must be interpreted with caution since the observed decline in FVC cannot be definitely attributed to SLB in the absence of a control group. However, our findings suggest that some decline in PFTs may occur in the period around the SLB even performed by VATS. This information should be shared with patients when contemplating to perform an SLB. Furthermore, PFTs should be repeated following the SLB and prior to initiating therapy, in order to inform subsequent monitoring of the disease.

Data on FVC changes in relation to performing an SLB are scarce. Daniil et al. [23] found no difference in lung function change in patients undergoing an SLB as compared to those who did not; however, only 33 patients had a VATS-SLB in their study, which included a variety of interstitial lung diseases [23].

The baseline clinical features (age, gender, and smoking status) in our cohort were comparable to most studies of IPF

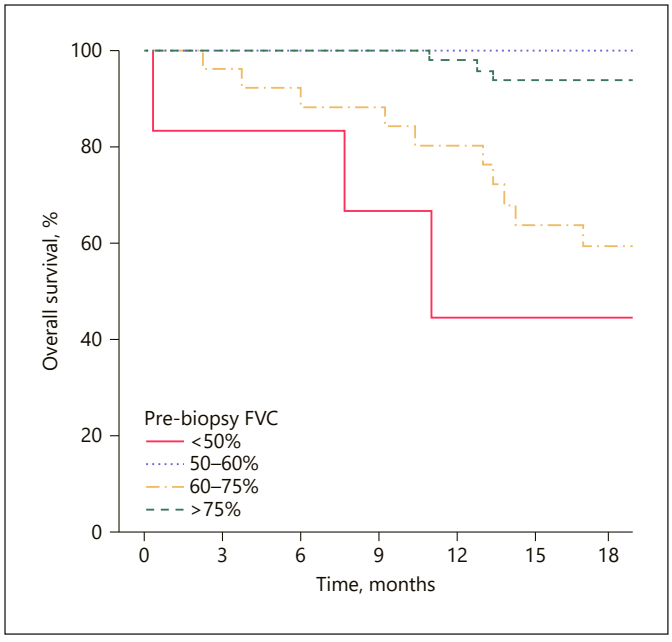

Fig. 2. Kaplan-Meier estimates of overall survival according to baseline FVC prior the lung biopsy (p value <0.001 between groups). FVC, forced vital capacity.

[1]. The functional characteristics tended to be better than older studies [6, 24], with a baseline FVC of 78% of predicted versus 65–70% and a DLCO of 53% of predicted versus 45% in older studies [6, 24]. This reflects the increasing attention given during the last decade not to perform an SLB in patients with impaired lung function, in whom the risk is increased [17]. However, 5.2% (6/115) patients in this series had an FVC <50% of predicted, 15.7% (14/89) had a DLCO <40%, and one had accelerated course of disease prior to the lung biopsy and would nowadays not undergo a biopsy.

Indeed, among patients with an FVC <50% who underwent a biopsy, one-third had an IPF exacerbation within 1 year, and half of them died within 1 year after the biopsy. It is difficult to attribute death to biopsy or to the natural course of the disease in these patients with advanced disease. However, the poor prognosis in patients with impaired lung function should lead to no longer consider a biopsy in such case. Conversely, the risk of SLB appeared to be minimal in subjects with an FVC >75% of predicted. No association between baseline FVC and IPF exacerbation in the subsequent year was found in univariate analysis, possibly due to the low number of events. An exercise test may allow for more accurate patient selection in subjects and may be considered prior to SLB, as routinely performed for lobectomies.

Comparison with published series of VATS is limited, as most of them included all etiologies of interstitial lung diseases, while the risk of acute exacerbation may be greater in IPF than in other fibrotic interstitial lung diseases [25]. However, the 30-day mortality rate was 1.7% (2 patients), strikingly similar to that found by Hutchinson et al. [26] in the UK [17] and consistent with what the same group found in the US from 2000 to 2011 [26]. In published series, the 30-day mortality of SLB ranges from 0% to 16.6% in the case of IPFs [27] and was 2.2% in a meta-analysis involving 2,148 patients with every type of interstitial lung diseases [28]. As expected, our study confirms that a low pulmonary reserve is associated with higher mortality at 1 year. Low DLCO was reported as a predictor of mortality of SLBs [12, 29]; however, often these included open lung thoracotomy. In our study, no statistically significant relationship was found between DLCO prior to biopsy and survival at 1 year. Seventeen patients (14.4%) experienced complications in the month following surgery, the rate and nature of which were comparable to the literature evaluating the morbidity of SLB to 12–30% [23, 26, 27, 30–32].

It is important to consider that practice has evolved over the study period spanning 10 years. As the risks of SLB are better known, indications and contraindications are considered much more carefully, and patients' selection for biopsy is now much more rigorous. The radiological criteria of UIP have been refined, and many patients would now be categorized as having UIP or probable UIP pattern at imaging, obviating the need for biopsy in the appropriate clinical context [9, 11].

This study has limitations inherent to its retrospective design, the relatively small sample size, and low number of events. Patients with diseases other than IPF were not included, which, however, increases homogeneity of the study population. In the absence of a control group, impairment of the lung function during the peri-biopsy period could not be definitely attributed to the biopsy or to the natural history of the disease. However, comparison to patients with IPF who did not undergo an SLB would be limited by groups not being quite comparable, and a controlled study is, therefore, deemed not feasible.

In conclusion, this study suggests that FVC decreases significantly after SLB, possibly more than the mean decline reported without treatment in the literature. It further shows significant morbidity and mortality when SLB is performed in patients with impaired lung function, although this could not be definitely attributed to the biopsy in this uncontrolled study. These findings reinforce that SLB should be restricted to low-risk patients with preserved lung function, in whom the results of the biopsy are definitely expected to alter management.

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Statement of Ethics

The study complied with the Declaration of Helsinki. This study was conducted under Reference Methodology MR004 [18] and was approved by the National Commission for Information Technology and Liberties of the Hospices Civils de Lyon (#17-251). In accordance with French legislation and the Hospices Civils de Lyon Research Ethics Committee, patients received a written information about the use of their data and their unrestricted right to remove them from the database.

Conflict of Interest Statement

The authors declare no conflict of interest in relation with the topic of this manuscript.

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Author Contributions

All authors fulfill the ICMJE criteria for authorship. V.C. and P.H.A. were responsible for design, analysis, and interpretation of data. All authors participated in data collection. P.H.A. and V.C. prepared the manuscript. All authors were responsible for manuscript review and revision. All authors approved the final version of the manuscript. The corresponding author (V.C.) had full access to all data in the study and had final responsibility for the decision to submit for publication.

Data Availability Statement

Individual de-identified participant data used for this study will be available for sharing with academic researchers for 5 years after publication of the present article upon request to the corresponding author accompanied by a research synopsis.

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