Longitudinal Forced Vital Capacity Monitoring as a Prognostic Adjunct after Lung Transplantation

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Abstract

Rationale: After lung transplantation, spirometric values are routinely followed to assess graft function. FEV₁ is used to characterize chronic allograft dysfunction, whereas the course of FVC change has been less acknowledged and rarely used.

Objectives: To better understand the temporal relationship and prognostic ability of FEV₁ and FVC decline after lung transplantation.

Methods: Serial FEV₁ and FVC values were studied among 205 bilateral lung transplant recipients. Different decline patterns were characterized and evaluated for prognostic value via restricted mean modeling of mortality and times to other pertinent events.

Measurements and Main Results: Baseline FEV₁ was achieved earlier than baseline FVC (median, 296 vs. 378 d; $P < 0.0001$). Decline in FEV₁ or FVC from their respective post-transplant baselines occurred in 85 patients (41%). Fifty-nine of 85 (69%) had an isolated FEV₁ decline, with 80% later meeting the FVC decline criterion. This subsequent FVC decline was associated with worsening FEV₁ and lower median survival. Twenty-five of 85 patients (29%) demonstrated concurrent FEV₁ and FVC decline. Patients with concurrent decline had higher 1- and 5-year mortality rates (1-yr, 53% vs. 18%, $P < 0.0001$; 5-yr, 61% vs. 48%, $P = 0.001$).

These patients were more likely to have rapid-onset of spirometry decline ($P = 0.05$) and lower FEV₁% predicted ($P = 0.04$) at presentation.

Conclusions: FVC decline from its post-transplant baseline provides valuable prognostic information. Concurrent FEV₁ and FVC decline identifies patients with fulminant, rapid deterioration and is the strongest clinical predictor of poor survival. Subsequent FVC decline in patients with an initial isolated FEV₁ decline identifies disease progression and portends poor prognosis.

Keywords: bronchiolitis obliterans; rejection; prognosis; chronic lung allograft dysfunction

At a Glance Commentary

Scientific Knowledge on the Subject: The course of FVC and predictive value of decline in this variable after lung transplantation has not been fully described.

What This Study Adds to the Field: Decline in FVC from its post-transplant baseline marks progression of graft dysfunction and predicts survival in bilateral lung transplant recipients. Standardized monitoring of FVC in combination with FEV₁ in lung transplant recipients should be considered.

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Long-term lung transplantation outcomes continue to be the worst among all solid organ transplants, with only a 20% 10-year survival (1). The major cause of long-term mortality is chronic graft dysfunction, which is predominantly monitored and detected by spirometry, an easily reproducible, consistent measure of lung function (2). Longitudinal FEV₁ monitoring with quantitation of change from baseline is used as a marker of allograft dysfunction because chronic graft failure after lung transplantation arises predominantly from small airway remodeling (3, 4). Approximately 50% of transplanted patients demonstrate persistent FEV₁ decline, defined as bronchiolitis obliterans syndrome (BOS), by 5 years (1). Further spirometric decline and post-BOS survival are variable; clinical factors including early or rapid-onset of BOS have been shown to predict both further decline in lung function and death (5, 6). Consideration of retransplantation or other aggressive measures is important in patients with a rapidly progressive course. Hence, defining other spirometric parameters that can help monitor graft failure and predict survival is of key significance.

FVC, a measure of exhaled lung volume, is another spirometric function routinely performed post-transplant. However, unlike FEV₁, FVC's temporal course is less well characterized, and no recommendations exist regarding parameters for monitoring FVC changes post-transplantation. Recent studies suggest that lung allografts can also develop restrictive allograft dysfunction secondary to parenchymal fibrosis, which may present as FVC decline (7, 8). Because worsening obstruction can also produce low FVC measurements (9), there is a need to understand temporal relationships between FEV₁ and FVC declines post lung engraftment.

In this study we investigate the spirometric patterns of changes in FEV₁ and FVC from their respective baselines post-lung transplantation and demonstrate that although the first spirometric change is consistently an FEV₁ decline, FVC decline from its baseline, either accompanying or after this FEV₁ decline, provides important prognostic information. Although validating the clinical use of following FVC, our data suggest caution in using FVC decline as

a surrogate for restrictive allograft dysfunction.

Methods

Patient Population

A total of 250 bilateral lung transplant recipients at the University of Michigan Health System between January 1996 and January 2014 formed the study group. Patients' clinical management followed a previously described lung transplant protocol (10). Those who died within 3 months or had less than or equal to five sets of spirometry values post-transplant were excluded (n = 45); 205 patients comprised the final cohort. Average cumulative rejection scores for A and B rejection were calculated by adding the ordinal numbers denoting the level of rejection present in each biopsy specimen in the first year post-transplant or before spirometric decline (whichever occurred first) and dividing by the total number of biopsies, as previously described (7, 11). Degree of HLA donor-recipient mismatching was calculated by summing the number of mismatches at the A, B, and DR loci. Patients were followed until death, retransplantation, or last recorded spirometry values. Vital status as of September 5, 2014, was determined by electronic patient chart review. The University of Michigan Institutional Review Board approved use of these data.

Spirometric Monitoring

Spirometry was performed according to American Thoracic Society guidelines at each clinic visit (2). After hospital discharge, clinic visits are initially scheduled every 2–3 weeks and then every 3 months, or earlier if clinically indicated. Baseline FEV₁ was defined per International Society for Heart and Lung Transplantation guidelines as the average of the two highest FEV₁ values obtained greater than or equal to 3 weeks apart post-transplant (3). Baseline FVC was calculated separately but in the same manner. Baseline FEV₁ and FVC dates were defined as the dates of the first measurements that contributed to the baseline FEV₁ and baseline FVC, respectively (4).

After 3 months had elapsed post-transplant, and after achievement of baseline spirometric values, patients were assessed for spirometric decline. Significant spirometric decline was defined as fall in

FEV₁, FVC, or both to less than 80% of the post-transplant baseline, measured by two consecutive FEV₁ and/or FVC values greater than or equal to 3 weeks apart in the absence of confounding variables in concordance with International Society for Heart and Lung Transplantation guidelines (4). One patient developed bronchial stenosis and was assigned new FEV₁ and FVC baseline values and times after the stenosis had stabilized.

Rapid-onset was defined as FEV₁ decline greater than 20% in the 6 months preceding the decline date as previously described (5). Early onset was defined as decline onset within 2 years post-transplant. BOS grades were defined as grades 1 (FEV₁ 66–80% of baseline), 2 (FEV₁ 51–65% of baseline), or 3 (FEV₁ ≤ 50% of baseline) (4).

Statistical Analysis

Statistical analyses were performed with R version 3.1.1. Categorical data were compared using chi-square or Fisher exact tests, as appropriate (12, 13). Continuous data were compared using two-sample *t* tests (14). Ordinal categorical variables were compared between groups via the Cochran-Armitage trend test (15). Medians to times to achieving baseline spirometry values were compared using the Wilcoxon signed rank test (16). Survival estimation was done via Kaplan-Meier curves (17). The log-rank test was used to compare survival differences between groups when hazards were proportional or nearly proportional (18). In group comparisons where a group had a higher event hazard than their counterpart during early follow-up that later transitions to a hazard lower than their counterpart (i.e., a violation of proportionality called crossing hazards), we used the Peto and Peto modification of the Gehan-Wilcoxon test (18). Informally, crossing hazards are a concern when early large differences between estimated survival curves attenuate over time. We used a common diagnostic for detecting deviations from proportionality that uses a plot of estimated log minus log survival probability curves for the groups being compared, with proportionality indicated when these curves are a constant distance apart across follow-up times.

Restricted mean survival models were used to compare expected days lived during 1- or 5-year follow-up periods based on multiple risk factors (19). This modeling

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram delineating study cohort, excluded patients, patients with confounding clinical conditions, and spirometric decline pattern groups. *Confounding clinical conditions included anastomotic complications ($n = 5$), acute rejection with improvement ($n = 2$), infection with improvement ($n = 4$), volume overload ($n = 3$), and other ($n = 3$).

paradigm is an alternative to the Cox proportional hazards model and is more appropriate with crossing hazards as seen in our data. Fold changes based on the 1- or 5-year restricted mean models indicate the multiplicative effect on the number of days lived in comparison with a reference group

(categorical variables) or based on a unit increase in the predictor (continuous variables) during that time period. We used cumulative incidence to illustrate the probability that a given patient would fall into each spirometric decline category before a given time (20). P values less than

Figure 2. Time to baseline FEV₁ and FVC after bilateral lung transplantation. Median times to baseline FEV₁ and FVC were significantly different (296 [interquartile range, 135–561 d] vs. 378 [interquartile range, 208–783 d]; $P < 0.0001$). One year after transplant, 60% (95% confidence interval [CI], 53–66%) of patients had met their baseline FEV₁, whereas only 48% (95% CI, 41–54%) had met their baseline FVC. At 3 years post-transplant, 91% (95% CI, 87–94%) of patients had met their baseline FEV₁, whereas 85% (95% CI, 80–90%) had met their baseline FVC ($n = 205$).

or equal to 0.05 were considered statistically significant in all models.

Results

Baseline FEV₁ and FVC Measurements after Lung Transplantation

Spirometric patterns post-lung transplantation were studied in the final cohort of 205 bilateral lung transplant recipients (Figure 1). The cohort had 5,249 spirometric observations in total during the follow-up period, with an average of nine spirometry measurements in the first year post-transplant. Median times to achieve FEV₁ and FVC baselines were 296 (interquartile range, 135–561) and 378 (interquartile range, 208–783) days, respectively; times to FEV₁ baseline were significantly shorter than times to FVC baseline ($P < 0.0001$) (Figure 2). Only 75 of 205 patients (37%) achieved both baselines on the same day. Most patients achieved FEV₁ baseline first (105 patients; 51%) rather than FVC baseline first (25 patients; 12%).

Patterns of Spirometric Decline

Eighty-five of 205 patients (41%) experienced a significant spirometric decline with a fall in FEV₁, FVC, or both to less than 80% of their post-transplant baseline values. An *a priori* decision was made to divide patients into three groups based on their initial spirometric decline event: “FEV₁ First” group (fall in FEV₁ with preserved FVC), “FVC First” group (fall in FVC with preserved FEV₁), and “Concurrent” group (fall in FEV₁ and FVC on the same date).

In 69% of the patients (59 of 85), the initial spirometric decline was an FEV₁ drop only. Twenty-nine percent of the patients (25 of 85) demonstrated a concurrent decline in both FEV₁ and FVC to less than 80% of their respective post-transplant baselines on the same date (Figure 3). Surprisingly, only one patient experienced an FVC drop with an initially preserved FEV₁. Figure 4 shows probabilities of entering the two predominant competing statuses (FEV₁ First or Concurrent groups) over time post-lung transplantation. During the first 4 years post-transplant, patients join the FEV₁ First or Concurrent groups at similar rates; however, after

Figure 3. (A) The course of FEV₁ and FVC values after lung transplantation in a representative patient from the “FEV₁ First” group is shown. The FEV₁ declines to less than 80% of the post-transplant baseline just before 3 years post-transplant; the FVC remains preserved but declines to less than 80% of the post-transplant baseline 511 days after FEV₁ decline. (B) The course of FEV₁ and FVC after lung transplantation in a representative patient from the “Concurrent” group is shown. Both FEV₁ and FVC decline on the same date 2.4 years after lung transplantation. Death occurred approximately 7 months later.

4 years, most patients follow the FEV₁ First decline pattern.

Clinical Features of Patients with FEV₁ First and Concurrent Decline Patterns

Demographic and clinical characteristics are shown in Table 1. The patients in the Concurrent group were significantly older than FEV₁ First patients (46 ± 12 vs. 40 ± 14 yr; $P = 0.05$) and had a lower FEV₁% predicted (FEV₁%pred) at initial spirometric decline ($49 \pm 16\%$ vs. $58 \pm 21\%$; $P = 0.04$). When FEV₁ was categorized

by BOS grading, Concurrent group patients had higher BOS grades at initial spirometric decline, with 32% classified as BOS grade 3 compared with 5% of FEV₁ First group patients ($P = 0.002$). Furthermore, more patients in the Concurrent group had rapid-onset of spirometric decline (84% vs. 59%; $P = 0.05$). A similar fraction of FEV₁ First and Concurrent group patients experienced weight gain greater than 10 lb between their FEV₁ baseline and decline and FVC baseline and decline, respectively. However, more patients in the Concurrent group had weight loss greater than 10 lb

between spirometric baseline and decline (see Table E1 in the online supplement). No significant difference was noted in recipient sex, lung allocation score (LAS), LAS diagnosis group, baseline FEV₁%pred, or A or B average cumulative rejection scores between groups. Similarly, there were no significant differences in cytomegalovirus donor-recipient mismatch status or HLA mismatch incidence between groups (see Tables E2 and E3). In summary, patients in whom the initial spirometric event was a concurrent FEV₁ and FVC fall had lower lung function at initial presentation and a higher likelihood of rapid-onset graft failure.

Pattern of Spirometric Decline as a Predictor of Mortality

Significant survival differences were noted after spirometric decline onset among FEV₁ First and Concurrent groups with a median survival of only 0.85 years in the Concurrent group compared with greater than 5 years in the FEV₁ First group (Figure 5). Concurrent group patients had a significantly decreased survival probability during the first post-spirometric decline year compared with the FEV₁ First group (47% [95% confidence interval (CI), 31–72%] vs. 82% [95% CI, 72–93%]; log-rank, $P = 0.0001$; Gehan-Wilcoxon, $P < 0.0001$). This difference remained significant through 5 years of follow-up with 52% (95% CI, 39–70%) of FEV₁ First group patients alive 5 years after spirometric decline compared with 39% (95% CI, 23–68%) of Concurrent group patients (Gehan-Wilcoxon, $P = 0.001$).

We further evaluated the impact of various clinical variables at the time of initial spirometric decline (donor and recipient age, sex, LAS, LAS diagnosis group, Concurrent vs. FEV₁ First decline pattern, FEV₁%pred at initial spirometric decline, rapid-onset, and early onset) on the number of days lived during 1 and 5 years of follow-up post-transplant by restricted mean modeling (Table 2). In univariate analysis, membership in the FEV₁ First group compared with the Concurrent group bestowed the benefit of 64% (95% CI, 39–94%; $P < 0.0001$) more days lived in the first year and 126% (95% CI, 38–270%; $P = 0.002$) more days lived at 5 years post-transplant. Twenty-nine percent of the variability for 1-year mortality results shown in Table 2 is explained by membership in the FEV₁ First group, twice

Figure 4. Cumulative incidence of entry into FEV₁ First group, Concurrent group, or death without entering either group. Early post-transplant, patients are more likely to die without entrance into the FEV₁ First or Concurrent groups. At 4 years, the probability of entrance into these groups is similar, but at 5 or more years post-transplant, a patient with a spirometric decline is most likely to have an FEV₁ First pattern of decline ($n = 205$).

as predictive as the next most influential variable, the FEV₁%pred at spirometric decline (adjusted R^2 , 14%). Higher FEV₁%pred at disease onset predicted more days lived; for every 10% increment higher FEV₁%pred at spirometric decline, there were an estimated 8% (95% CI, 4–13%; $P = 0.001$) and 27% (95% CI, 13–42%; $P < 0.0001$) more days lived during 1 and 5 years of follow-up, respectively. In multivariate analysis, membership in the

FEV₁ First group and FEV₁%pred at spirometric decline continued to be significant predictors of the time lived after spirometric decline (Table 3).

Predictors and Significance of FVC Decline in the FEV₁ First Group

Eighty percent (47 of 59) of patients in the FEV₁ First group demonstrated a subsequent FVC decline to less than 80% of their baseline value. Time to

FVC decline is shown in Figure 6A. Six months after FEV₁ decline, nearly 50% of these patients had already experienced a subsequent FVC decline, reaching 64% 1 year after FEV₁ decline. At the time of FVC decline, a significant progression in BOS grade was noted with the percentage of patients with BOS grade greater than or equal to two increasing from 36 to 83%. An average further decline in FEV₁%pred of 13% (0.44 L) occurred from the time of FEV₁ to FVC drop ($P = 0.004$). Figure 6B illustrates the distribution of further FEV₁ decline at FVC decline time in this patient group. FVC decline predictors were studied by restricted mean modeling (Table 4). Lower FEV₁%pred and higher BOS grade predicted an earlier fall in FVC in the univariate model. For every 10% increment higher FEV₁%pred at initial spirometric decline, there were 21% more days (95% CI, 3–43%; $P = 0.03$) before FVC decline. Patients with BOS grade 1 at diagnosis had 155% more days (95% CI, 28–408%; $P = 0.01$) until FVC drop compared with patients with initial grades 2 or 3 BOS. These data suggest that time to FVC decline is linked to obstruction severity.

Subsequently, we investigated the impact of FVC decline in determining patient outcomes in this group. Time to death after

Table 1. Demographic and Clinical Characteristics of Patients with Spirometric Decline According to Group Status

	FEV ₁ First Group ($n = 59$)	Concurrent Group ($n = 25$)	<i>P</i> Value
Age at transplant, yr*	40 (± 14)	46 (± 12)	0.05
Male	35 (59%)	12 (48%)	0.47
Donor age, yr*	33 (± 13)	35 (± 16)	0.74
LAS score*	46 (± 20)	47 (± 18)	0.89
LAS group			
Group A	20 (34%)	8 (32%)	1.00
Group B	2 (3%)	3 (12%)	0.15
Group C	19 (32%)	6 (24%)	0.60
Group D	18 (31%)	8 (32%)	1.00
Ischemic time, min*†	610 (± 103)	647 (± 111)	0.22
Early onset	29 (49%)	9 (36%)	0.39
Rapid-onset	35 (59%)	21 (84%)	0.05
FEV ₁ % predicted at baseline*	87 (± 24)	88 (± 15)	0.71
FEV ₁ % predicted at initial spirometric decline*	58 (± 21)	49 (± 16)	0.04
BOS grade at initial spirometric decline			
Grade 1	37 (63%)	8 (32%)	0.02
Grade 2	19 (32%)	9 (36%)	0.80
Grade 3	3 (5%)	8 (32%)	0.002
Average cumulative A rejection score*‡	0.21 (± 0.27)	0.31 (± 0.28)	0.12
Average cumulative B rejection score*‡	0.05 (± 0.11)	0.06 (± 0.12)	0.56

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; LAS = lung allocation score.

*Mean (SD).

†Ischemic time = total ischemic time for bilateral lungs.

‡Each patient's average cumulative rejection score is calculated by adding the ordinal values of each biopsy specimen's A or B score divided by the total number of biopsies performed in the first year post-transplant or before spirometric decline, whichever occurs first.

chronic lung allograft dysfunction (4). However, no specific guidelines exist regarding FVC measurements, and FVC course after lung transplantation remains to be fully elucidated. In this study, we examine the relationship between FEV₁ and FVC spirometric decline patterns from their respective post-transplant baselines and their impact on predicting survival after bilateral lung transplantation. We demonstrate that times to highest FEV₁ and FVC values post-transplant are variable with FVC baseline values established later in a patient's course.

A decline in spirometry from post-transplant baseline was found to demonstrate two predominant patterns: an initial fall in FEV₁ alone followed by an FVC decline with disease progression, or a concomitant fall in FEV₁ and FVC. Although isolated FVC fall was rarely the first event, change in FVC was shown to provide key prognostic information. We demonstrate that an initial spirometric presentation with a concurrent FEV₁ and FVC decline from their respective baselines portends a very poor prognosis with a 1-year mortality rate greater than 50%. This pattern was significantly associated with a rapid onset and lower FEV₁%pred at presentation. We further demonstrate that in patients with an initial FEV₁ decline only, subsequent FVC decline below 80% of its baseline is associated with worsening FEV₁ and offers an important clinical marker of lower median survival. These are important spirometric events that can be

Figure 5. Survival probability according to FEV₁ First versus Concurrent group status at (A) 1 and (B) 5 years after spirometry decline. The number of patients at risk at each time point is listed below the figure. One-year survival probability after initial spirometry decline in the FEV₁ First group was 82% compared with 47% in the Concurrent group. Five years after significant spirometry decline, this difference was smaller but remained statistically different, with 52% of patients in the FEV₁ First group alive compared with 39% of patients in the Concurrent group.

FVC decline is shown in Figure 7A. Although median survival in the FEV₁ First group from initial spirometry decline was greater than 5 years, median survival post-FVC decline was only 2.8 years. In those patients in the FEV₁ First group who had a subsequent FVC drop, BOS grade did not confer any further statistically significant information about mortality (1 yr, $P = 0.85$; 5 yr, $P = 0.16$). Survival after FVC decline in the FEV₁ First group was compared with survival in the Concurrent group. Although

survival remained different through 2 years post-FVC drop, survival differences are negligible beyond that time point (Figure 7B).

Discussion

Post-lung transplantation graft function is primarily monitored by spirometry, and a persistent FEV₁ decline from its post-transplant baseline is used to identify

Table 2. Univariate Restricted Mean Analysis Evaluating Ability of Given Variables to Predict Days Lived at 1 and 5 Years after Spirometry Decline (n = 84)

Variable	1 yr		5 yr	
	Fold Change (95% CI)	P Value	Fold Change (95% CI)	P Value
Recipient age, per 20-yr increment	0.94 (0.82–1.08)	0.37	0.97 (0.68–1.39)	0.86
Donor age, per 20-yr increment	1.09 (0.95–1.25)	0.24	1.26 (0.88–1.80)	0.22
Recipient sex, male	0.96 (0.8–1.16)	0.68	0.81 (0.50–1.31)	0.39
LAS score, per 10-point increment	1.00 (0.95–1.06)	0.92	1.11 (0.95–1.28)	0.19
LAS Group B*	1.08 (0.72–1.62)	0.72	1.01 (0.34–2.96)	0.99
LAS Group C*	0.93 (0.74–1.18)	0.57	0.85 (0.46–1.57)	0.60
LAS Group D*	0.97 (0.77–1.22)	0.81	0.99 (0.54–1.82)	0.98
FEV ₁ First group	1.64 (1.39–1.94)	<0.0001	2.26 (1.38–3.70)	0.002
FEV ₁ % predicted at initial spirometric decline, per 10% increment	1.08 (1.04–1.13)	0.001	1.27 (1.13–1.42)	<0.0001
Early onset	1.02 (0.85–1.22)	0.84	1.04 (0.64–1.68)	0.89
Rapid-onset	0.84 (0.70–1.02)	0.09	0.68 (0.41–1.12)	0.13
BOS grade 1 at initial spirometric decline	1.32 (1.11–1.57)	0.002	2.08 (1.32–3.27)	0.002

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; CI = confidence interval; LAS = lung allocation score.

*Compared with LAS Group A.

Table 3. Multivariate Restricted Mean Analysis Evaluating the Ability of Given Variables to Predict Days Lived at 1 and 5 Years after Spirometry Decline (n = 84)

	1 yr		5 yr	
	Fold Change (95% CI)	P Value	Fold Change (95% CI)	P Value
Recipient age, per 20-yr increment	0.90 (0.77–1.05)	0.19	0.84 (0.54–1.30)	0.43
LAS Group B*	1.23 (0.88–1.72)	0.23	1.22 (0.46–3.19)	0.69
LAS Group C*	0.86 (0.67–1.09)	0.21	0.78 (0.39–1.57)	0.49
LAS Group D*	1.06 (0.87–1.30)	0.54	1.39 (0.79–2.47)	0.26
FEV ₁ First group	1.53 (1.28–1.83)	<0.001	1.74 (1.04–2.91)	0.04
FEV ₁ % predicted at initial spirometric decline, per 10% increment	1.07 (1.02–1.12)	0.01	1.27 (1.11–1.46)	0.001
Rapid-onset	1.04 (0.87–1.24)	0.66	1.17 (0.70–1.96)	0.55
BOS Grade 1 at initial spirometric decline	1.07 (0.89–1.27)	0.49	1.22 (0.73–2.04)	0.45

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; CI = confidence interval; LAS = lung allocation score.

Adjusted R^2 , 0.41 at 1 year and 0.28 at 5 years.

*Compared with LAS Group A.

used for clinical prognostication and suggest that monitoring FVC decline in a manner similar to FEV₁ should be used in clinical practice.

We report differences in times to achieving baseline FEV₁ and FVC values after bilateral lung transplantation. Calculation of patient-specific baseline lung volumes is important in following graft function because the highest graft function attained after transplantation is variable (21). Subsequent spirometric values are then compared with the post-transplant baseline. However, this approach has

predominantly been used for FEV₁; FVC trajectory is not well characterized (21). Temporal FEV₁ and FVC evaluation here demonstrated that in most (63%) patients, highest FEV₁ and FVC values were noted at separate times post-lung transplantation. This novel demonstration that FVC baseline values are rarely achieved concomitantly with FEV₁ baselines is important, because generally FVC values at the time of highest FEV₁ values are used as baselines (7, 22). Studying graft function by comparing FEV₁ and FVC with their respective baseline values separately offers

a more relevant method and should be considered in future investigations.

We demonstrate that longitudinally following FVC trajectory provides key prognostic information and adds significantly to data obtained from FEV₁ course post-lung transplantation, the approach presently used for evaluating graft function and predicting outcomes. An initial spirometric presentation of concomitant FEV₁ and FVC fall from their respective individual baselines was shown to portend a very poor long-term outcome with median survival of less than 1 year. This finding is clinically relevant because the extremely high 1-year mortality (53%) warrants early consideration of retransplantation or other aggressive measures.

The consequences of FVC decline in patients at the time of FEV₁ decline have been evaluated in two recent studies (7, 22), although in both studies FVC at FEV₁ decline was compared with FVC at maximal FEV₁ values, not a true FVC baseline. A sentinel observation by Sato and coworkers (8) demonstrating that patients with FEV₁ fall who had a TLC less than 90% of baseline, termed restrictive allograft syndrome (RAS), have worse survival generated this interest in FVC. Woodrow and coworkers (22) evaluated patients with either the presence or absence of parenchymal abnormalities; in those without parenchymal abnormalities, BOS patients without FVC decline had no survival advantage compared with patients with FVC decline. To potentially identify a RAS phenotype by spirometry, Todd and

Figure 6. (A) Proportion of patients in the FEV₁ First group demonstrating a subsequent significant FVC decline (2 consecutive values ≥ 3 wk apart that fall below 80% of the post-transplant FVC baseline). By 1 year, 64% of patients had experienced a significant decline in their FVC. At 3 years, FVC had significantly declined in 86% of patients (n = 59). (B) Decline in FEV₁% predicted by the time of FVC drop in FEV₁ First group patients. Most patients in the FEV₁ First group had a further decline in their FEV₁ at the time that FVC declined to less than 80% of the post-transplant baseline. Only three patients did not have a further decline in FEV₁. On average, a patient's FEV₁ declined 0.44 L (13%) at the time of FVC decline (n = 47).

Table 4. Univariate Restricted Mean Analysis Evaluating the Ability of Given Variables to Predict Days before FVC Decline in the FEV₁ First Group (n = 47)

Variable	Fold Change (95% CI)	P Value
Recipient age, per 20-yr increment	0.89 (0.53–1.50)	0.66
LAS Group B*	0.28 (0.04–1.99)	0.21
LAS Group C*	0.53 (0.23–1.24)	0.15
LAS Group D*	0.46 (0.19–1.08)	0.08
FEV ₁ % predicted, per 10% increment, at initial spirometric decline	1.21 (1.03–1.43)	0.03
BOS grade 1 at initial spirometric decline	2.55 (1.28–5.08)	0.01
Rapid-onset	0.90 (0.44–1.85)	0.77

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; CI = confidence interval; LAS = lung allocation score.

*Compared with LAS Group A.

coworkers (7) defined patients as restrictive chronic lung allograft dysfunction if an FVC decline was present at the time of FEV₁ fall (BOS onset). The incidence of concurrent decline in this study was similar to that noted in our cohort (~30%), and these patients with FVC decline at the time of FEV₁ decline also had significantly worse survival. Our study reiterates the value of using FEV₁ and FVC to identify a clinical phenotype associated with poor survival (7).

The mechanism underlying the Concurrent group's poor prognosis remains an important question, and our comparison of the Concurrent and FEV₁ First groups

offers insight. Two key differences existed between these groups. First, Concurrent group patients had a lower FEV₁%pred at diagnosis. Second, they were more likely to have rapid-onset of disease with decline in FEV₁ by greater than 20% in the preceding 6 months. These differences highlight that Concurrent patients had more precipitous and severe FEV₁ declines. As airway obstruction worsens, premature airway closure prevents full expiration, resulting in FVC decline (9, 23, 24). Interestingly, similar to patients with severe obstructive lung disease, a higher proportion of Concurrent group patients also demonstrated significant weight loss at

the time of spirometric decline (25, 26). Woodrow and coworkers (22) considered the possibility that FVC decline in BOS patients could arise from worsening hyperinflation or complete obliteration of distal airways, and reported that patients designated as BOS had a concurrent FVC decline averaging 20%, identical to those patients with a radiographically defined restrictive process. Contrarily, Todd and coworkers (7) have suggested that a concurrent FEV₁ and FVC decline identifies patients with RAS. However, even in their study, nearly half of the patients with concomitant decline were classified as severe-onset, defined by the authors as FEV₁ less than or equal to 65% of the post-transplant baseline at the time of disease onset. Furthermore, 67% of these patients with pathology available had "histologically inactive constrictive bronchiolitis" (7, 27).

On further review of our cohort of Concurrent patients' clinical courses, we noted that 6 of 15 patients (40%) who had died in this group had documented severe hypercarbic respiratory failure. These findings suggest that patients with concurrent FEV₁ and FVC decline may not uniformly have a physiologic process distinct from BOS driving their pulmonary decline. Caution should be exercised in labeling these cases as RAS or restrictive chronic lung allograft dysfunction without further data, such as histology or TLC (28). However, future multicentric prospective trials with inclusion of full pulmonary function testing and radiologic measures of parenchymal disease and airway remodeling at the time of spirometric decline are needed to fully evaluate the underlying pathophysiology behind these distinct clinical presentations.

This study characterizes for the first time the course of FVC over time in patients presenting with an isolated FEV₁ decline. Eighty percent of FEV₁ First group patients subsequently demonstrated a significant FVC fall. Notably, FEV₁%pred at initial spirometric decline was a significant predictor of time to FVC drop, because patients with higher FEV₁%pred demonstrated longer times to FVC drop. At the time of FVC decline, almost all patients had a further decline in FEV₁%pred. These findings demonstrate that FVC decline is associated with FEV₁ fall severity and further supports the notion that FVC decline in isolation without

Figure 7. (A) Survival probability after FVC decline in the FEV₁ First group patients who experienced a subsequent FVC decline (n = 47). (B) Survival probability of the FEV₁ First group patients who had a subsequent FVC decline as compared with Concurrent group patients.

Figure 8. Prognostic value of spirometric decline patterns after lung transplantation. Patients who initially experienced an isolated FEV₁ decline had higher 1- and 5-year survival probabilities than patients with a concurrent decline in FEV₁ and FVC. A subsequent FVC decline in patients with an initial FEV₁ decline predicted decreased 1- and 5-year survival.

knowledge of TLC cannot be used as a RAS surrogate. Median survival was much lower after FVC drop, and BOS grade did not confer any further statistically significant information about mortality at this stage, suggesting that FVC decline can provide a simple, concrete spirometric variable to caution the clinician regarding worsening prognosis.

Characterization of further course and predicted survival after initial evidence of graft functional decline is of paramount significance in patient selection and stratification in clinical trial designs. It has been demonstrated that decline rate after onset of physiologic abnormalities (BOS) is highly variable; some patients progress rapidly, whereas others decline minimally in the same time period, with rapidity, severity, and timing of initial FEV₁ decline predicting subsequent FEV₁ course

and survival (5, 6, 29). Higher BOS grades and transition from lower to higher grades have been shown to correlate with worsened survival (30, 31). Recent data have also used TLC and radiographic changes to characterize subsets with poor survival (8, 32). However, full pulmonary function testing is not routinely performed for graft surveillance, and radiographic interpretations can vary; presently no specific guidelines or consensus exist regarding use of high-resolution computed tomography other than ruling out confounding variables (33). Hence, the ability to characterize distinct clinical phenotypes based on spirometry, as suggested by the present study, has a distinct advantage.

It is important to note that FEV₁ First group membership was independently associated with more days

lived at both 1 and 5 years after accounting for BOS grade, FEV₁ at spirometric decline, and rapid-onset BOS. Thus, FVC decline was predictive even in the setting of knowledge of these other characteristics; a patient in the FEV₁ First group who has the same FEV₁% predicted at spirometric decline as a patient in the Concurrent group will live longer because of group membership and the fact that their FVC has not yet declined at BOS diagnosis. The Concurrent group's independent and close relationship with time to death was evidenced by the higher hazard ratios and lower *P* values. As noted in Table 3, Concurrent group members had increased mortality at 1 year, which was more statistically significant (*P* < 0.001) than other covariates in the model, such as FEV₁%pred at spirometry decline (by 10% increments) (*P* = 0.01). Rapid-onset and BOS grade were not significant predictors of time to death in this multivariate model. Thus, FVC decline concomitant with FEV₁ decline (Concurrent group membership) is not only the strongest predictor of mortality at 1 year but provides prognostic information that is independent of FEV₁ or BOS stage.

Knowledge of the spirometric group and potential stratification by this variable needs to be considered in future clinical trials so as to minimize confounders in interpretation of therapeutic response. However, it should be recognized that FVC data use has been limited to bilateral lung transplant recipients in both our study and previous investigations (7). Also, because these physiologic markers are not complete surrogates for the presence, severity, and topography of underlying fibroproliferation, development of advanced imaging techniques and/or biomarkers to allow for proper patient selection for potential therapeutic options remains necessary.

In summary, we demonstrate that FVC, a readily available clinical parameter, can be a very useful adjunct to FEV₁ in following graft function and predicting survival after bilateral lung transplantation. Calculation of true FVC baseline to determine fall cutoffs is validated for the first time with demonstration that peak FVC values are generally attained later than peak FEV₁ values. A simple algorithm can be used

based on survival rates noted in these spirometric groups, as highlighted in Figure 8. A persistent (≥ 3 wk apart), concomitant decline in FEV₁ and FVC to less than 80% of their respective

baseline values identifies a high-risk group with poor 1-year survival. In patients who present with initial decline in FEV₁ alone, a subsequent fall in FVC can be used for prognostic stratification as

a marker of disease progression and severity. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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