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Supranormal Expiratory Airflow after Bilateral Lung Transplantation Is Associated with Improved Survival

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Rationale: **Flow volume loops (FVL) in some bilateral lung transplant (BLT) and heart–lung transplant (HLT) patients suggest variable extrathoracic obstruction in the absence of identifiable causes. These FVLs usually have supranormal expiratory and normal inspiratory flow rates (SUPRA pattern).**

Objectives: **Characterize the relationship of the SUPRA pattern to predicted donor and recipient lung volumes, airway size, and survival.**

Methods: **We performed a retrospective review of adult BLT/HLT patients. We defined the SUPRA FVL pattern as: (*1*) mid-vital capacity expiratory to inspiratory flow ratio (Ve50:Vi50) > 1.0, (*2*) absence of identifiable causes of extrathoracic obstruction, and (*3*) Ve50/FVC $\geq 1.5\ s^{-1}$. We calculated predicted total lung capacity (pTLC) ratio by dividing the donor pTLC by the recipient pTLC. We measured airway luminal areas on thoracic computer tomographic scans. We compared survival in patients with and without the SUPRA pattern.**

Measurements and Main Results: **The SUPRA FVL pattern occurred in 56% of the 89 patients who qualified for the analysis. The pTLC ratio of SUPRA and non-SUPRA patients was 1.11 and 0.99, respectively ($P = 0.004$). A higher pTLC ratio was correlated with increased probability of the SUPRA pattern ($P = 0.0072$). Airway luminal areas were larger in SUPRA patients ($P = 0.009$). Survival was better in the SUPRA cohort ($P = 0.009$).**

Conclusions: **The SUPRA FVL pattern was frequent in BLT/HLT patients. High expiratory flows in SUPRA patients could result from increased lung elastic recoil or reduced airway resistance, both of which could be caused by the pTLC mismatch. Improved survival in the SUPRA cohort suggests potential therapeutic approaches to improve outcomes in BLT/HLT patients.**

Keywords: lung transplantation; flow volume loops; lung size mismatch; dysanapsis; surface tension

Pulmonary function tests (PFT) with flow volume loops (FVL) are important for the detection of allograft rejection and other pulmonary complications after lung transplantation. The FVL ratio of the expiratory flow at mid-vital capacity (Ve50) to the inspiratory flow at mid-vital capacity (Vi50) is useful to detect obstructive lesions of the laryngotracheal airway (1, 2). Ve50 is usually on an effort-independent part of the expiratory flow volume curve, and Vi50 occurs in the middle of the inspiratory effort, where it is not affected by rapid acceleration or deceleration of flow. Thus Ve50:Vi50 captures the different effects of intra- or extrathoracic obstruction on inspiratory and expiratory flows. Extrathoracic airway obstruction causes decreased inspiratory airflow. Therefore, Ve50:Vi50 > 1.0 suggests variable extrathoracic obstruction (1–3). We noted that Ve50:Vi50 frequently exceeded 1.0 in our bilateral lung transplant (BLT) and heart lung (HLT) transplant patients. However, this pattern was usually caused by high Ve50, not low Vi50 (Figure 1). We therefore defined this FVL pattern without anatomic evidence for extrathoracic obstruction as the supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern (SUPRA FVL). Supranormal expiratory flow after BLT/HLT has been described previously (4, 5), but we are not aware of reports of pseudo-variable extrathoracic obstruction. We speculated that the SUPRA FVL pattern could occur if smaller donor lungs were transplanted into a larger recipient thorax. This could increase lung tissue elastic recoil at any lung volume and therefore increase expiratory airflow (6). However we found that a major predictor of the SUPRA FVL pattern was the opposite: larger donor lungs relative to the predicted volume of the recipient thorax. We define the SUPRA FVL pattern and describe its frequency, airway anatomy, physiology, and clinical implications in a cohort of BLT/HLT patients. Some of the results of these studies have been previously reported in the form of an abstract (7).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Flow volume loops (FVL) in some bilateral lung and heart–lung transplant patients show supranormal expiratory flow and suggest variable extrathoracic obstruction in the absence of identifiable causes.

What This Study Adds to the Field

We defined the supranormal expiratory flow FVL pattern (SUPRA FVL). The SUPRA pattern occurred in more than 50% of patients, especially early after transplant. Restriction of donor lungs in a relatively smaller recipient thorax is associated with this FVL pattern. The SUPRA pattern could be caused by increased lung elastic recoil or decreased airway resistance from relatively larger transplanted airways. The association with improved survival deserves further investigation, which could lead to new therapeutic strategies to improve clinical outcomes in lung transplant patients.

METHODS

We analyzed all adult BLTs and HLTs performed at Johns Hopkins Hospital (JHH) between January 1, 2000 and December 31, 2008. Single-lung transplant recipients were not assessed due to the potential impact of the native lung on overall lung function. All adult BLT and

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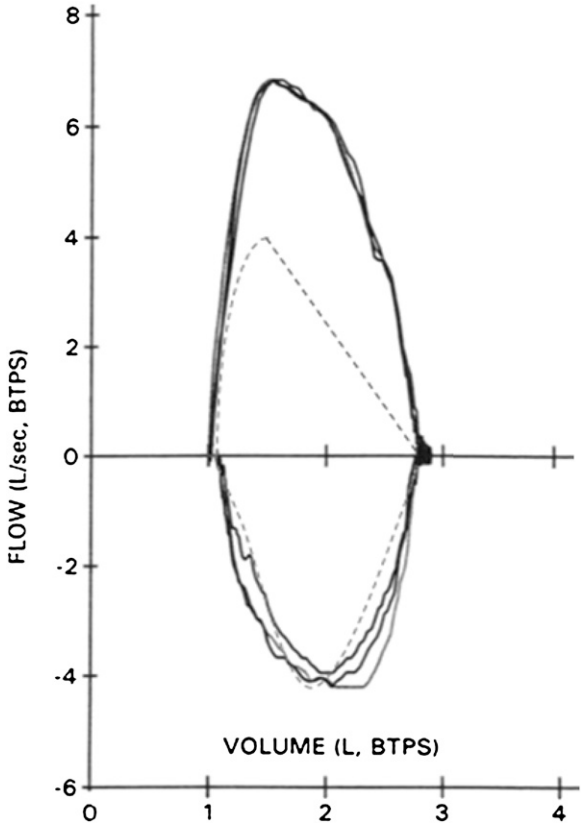

Figure 1. Flow volume loops of a 65-year-old female patient 2 years after bilateral lung transplantation for cystic fibrosis, exemplifying the supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern (SUPRA FVL pattern). The criteria of the SUPRA pattern are fulfilled by: (*1*) ratio of the maximal expiratory mid-vital capacity flow to the maximal inspiratory mid-vital capacity flow (Ve50:Vi50) of greater than 1.0 (the ratio is 1.5), (*2*) absence of identifiable causes of extrathoracic obstruction, (*3*) supranormal expiratory flow with a Ve50/FVC ratio of at least 1.5 s^{-1} (the Ve50/FVC is 3.21 s^{-1}), and (*4*) reproducibility in at least two FVLs. *Dashed line* indicates expected expiratory flow rates. BTPS = Body Temperature Pressure Saturated.

HLT recipients alive 3 months after transplantation with at least two post-transplant FVLs were included in this study, which was approved by the Institutional Review Board. All included patients had spirometry, FVLs, and fiberoptic bronchoscopy (FOB) according to the institutional lung transplant protocol (*see* online supplement). We defined the SUPRA FVL pattern as: (*1*) Ve50:Vi50 > 1.0, (*2*) supranormal expiratory flow with a Ve50/FVC $\geq$ 1.5 s^{-1}, (*3*) reproducibility in at least two FVLs obtained on separate days, and (*4*) absence of known causes of variable extrathoracic obstruction after review of FOB reports, medical records, and the lung transplant database. Bronchiolitis obliterans syndrome (BOS) and acute rejection were diagnosed according to the standard International Society of Heart and Lung Transplant criteria (8). An otherwise unexplained greater than 20% decrease from best post-transplant FEV_1 was used to diagnose the onset of BOS. Airway complications were defined as anastomotic or lower airway stenosis or bronchomalacia that required dilatation, stent implantation, laser therapy, or endoscopic follow-up.

Analysis of FVLs

The FVLs were analyzed according to time intervals at 1 to 6, 6 to 12, 12 to 24, 24 to 36, and more than 36 months. For any given interval, if there were multiple FVLs available, the one showing a SUPRA pattern and/or the one with the highest FVC was included. For each patient also the FVL with the highest FEV_1/FVC ratio was selected (Best-FVL). Time constant estimate Tau* ($-1/\ln[1 - FEV_1/FVC]$), Tau** (FVC/[2 × Ve50]), and a slope estimate (Ve50/[0.5 × FVC]) were calculated for FVLs of the 1 to 6 month time interval and for Best-FVLs (9).

Calculation of the Predicted Total Lung Capacity Ratio

The predicted total lung capacity ratio (pTLC) of all donors and recipients was calculated using regression equations based on height and sex (10). For each individual patient, size matching between donor lungs and recipient thorax was expressed as a ratio of donor pTLC to recipient pTLC (pTLC ratio).

Thoracic Computer Tomographic Airway Analysis

CT scans had been obtained for clinical reasons in some patients. Selection was based on timing (3–6 mo post-transplant, performed 2007 or later) and absence of airway complications or significant pleural pathology. Airway dimensions were derived from airway luminal area measurements as previously described and validated (11, 12). Details about the individual CT scans are summarized in Table E1 and part 3 in the online supplement.

Validation Cohort

All adult BLT/HLT patients transplanted at Inova Fairfax Hospital, Fairfax, Virginia, with at least two FVLs after transplantation, were included in the validation cohort to assess the frequency of the SUPRA FVL pattern and its relation to clinical outcomes. Institutional Review Board approval was obtained.

Statistical Analysis

Numeric results are expressed as mean ± SD. Comparisons between two groups were made with a two-tailed *t* test, assuming equal variances; one-way analysis or variance; or Fisher exact test as appropriate. Least squares regression models were constructed with the JMP software program to relate pTLC mismatch and pulmonary function (www.jmpdiscovery.com). Survival and freedom from BOS were assessed by the Kaplan-Meier method. We evaluated the impact of the SUPRA pattern on long-term survival using univariable and multivariable Cox proportional hazards models. A *P* value less than 0.05 was considered significant.

RESULTS

Characteristics of the Johns Hopkins Study Population

There were 107 adult patients who qualified for the analysis, of whom 99 received a BLT and 8 an HLT (Table 1). Eighty-nine

TABLE 1. CHARACTERISTICS OF 107 ADULT BILATERAL LUNG AND HEART–LUNG TRANSPLANT PATIENTS TRANSPLANTED AT THE JOHNS HOPKINS HOSPITAL BETWEEN JANUARY 1, 2000 AND DECEMBER 31, 2008

Characteristics	All	Included	Excluded	*P* Value*
Demographics				
No.	107	89	18	—
Sex	48 M, 59 F	38 M, 51 F	10 M, 8 F	0.65
Age, yr (SD)	44.8 (14.0)	44.5 (14.1)	46.5 (13.8)	1.0
Transplant indication				
Cystic fibrosis	27	23	4	1.0
COPD	23	23	—	0.011
Pulmonary hypertension	12	9	3	0.42
Sarcoidosis	6	5	1	1.0
Interstitial lung disease	21	15	6	0.12
Congenital heart disease (HLT)	8	5	3	0.13
Other	10	9	1	1.0
Post transplant				
No. of PFTs (SD)	21 (17)	25 (15)	0 (1)	0.023
No. of FOBs (SD)	8 (6)	9 (5)	3 (9)	0.44

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; F = female; FOB = fiberoptic bronchoscopy; HLT = heart–lung transplant; M = male; PFT = pulmonary function test.

* Comparison of included and excluded patients.

(83%) were alive at 3 months and had at least two FVLs available for review. The most common reason for exclusion was death before 3 months after transplantation (14 patients). Follow-up was complete until time of death or June 28, 2009, with a mean follow-up period of 3.0 years (range 0.4–9.3 yr). The data set included 2,206 FVL observations.

Frequency, Time Course and Demographics of the SUPRA FVL Pattern

The SUPRA FVL pattern occurred in 50 of the 89 patients analyzed (56%) (Table 2). The mean number of FVLs in the SUPRA cohort was 27 ± 15 and 22 ± 14 in the NON-SUPRA cohort. On average 6 ± 4 FVLs in the SUPRA cohort demonstrated the SUPRA pattern. The SUPRA pattern occurred early in the post-transplant period. At 1 to 6 months after BLT/HLT, 86 of 89 patients had FVL for review and 47 (55%) displayed this FVL pattern. At subsequent time points the SUPRA pattern was less frequent (32% for 6–12 mo, 16% for 12–24 mo, 12% for 24–36 mo, and 14% for > 36 mo; Figure 2). The mean ages, body mass index, number of FVLs, and FOBs of the patients in the SUPRA and NON-SUPRA cohorts were similar (Table 2). All the HLT patients included in the analysis displayed the SUPRA pattern (n = 5). Among the different primary diseases, fewer patients with interstitial lung disease displayed the SUPRA pattern (6% vs. 31%, $P = 0.012$), but there was no difference in the distribution of patterns among the other primary diseases (Table 2).

Lung Function Characteristics

Spirograms showed lower FVCs in the SUPRA compared with the NON-SUPRA cohort until 24 months after transplant ($P < 0.05$) (Figure E3, Table E2). SUPRA patients showed a moderate reduction in FVC at 1 to 6 months (63.2 ± 17% of predicted). FVC increased over time to 77.4 ± 24% of predicted at 12 to 24 months and remained mildly reduced at greater than 36 months (81.2 ± 21% of predicted). Patients in the NON-SUPRA cohort tended to have higher FVCs than SUPRA patients until 24 months (69.8 ± 21% at 1–6 mo and 83.8 ± 18% at 12–24 mo, comparisons to SUPRA $P = 0.15$ and $P = 0.14$, respectively), but FVCs were comparable after 24 months ($P = 0.94$). There was a significant difference in the FEV_1/FVC ratio between the cohorts at 1 to 6 months (SUPRA, 0.964 ± 0.05 vs. NON-SUPRA, 0.758 ± 0.06, $P < 0.001$; Table 2). Maximal expiratory airflows at all lung volumes were higher in the SUPRA cohort ($P < 0.001$; Table 2, Figure 3A]). In both cohorts expiratory flows decreased over time. However, these

TABLE 2. CHARACTERISTICS OF PATIENTS IN THE JOHNS HOPKINS HOSPITAL COHORTS

Characteristic	SUPRA	NON-SUPRA	*P* Value
Demographics			
No. (%)	50 (56)	39 (44)	—
Sex	19 M, 31F	19M, 20 F	0.39
Age, yr (SD)	44.2 (14.8)	44.1 (14.1)	1.0
Height, m (SD)	1.64 (0.08)	1.72 (0.1)	0.0014
Weight, kg (SD)	59.3 (13)	62.8 (12)	0.33
Body mass index (SD)	21.8 (4.3)	21.5 (3.5)	1.0
Transplant Indication			
Cystic fibrosis (%)	14 (28)	9 (23)	0.63
COPD (%)	12 (24)	11 (28)	0.81
Pulmonary hypertension (%)	6 (12)	3 (8)	0.73
Sarcoidosis (%)	4 (8)	1 (3)	0.38
Interstitial lung disease (%)	3 (6)	12 (31)	0.012
Congenital heart disease (HLT) (%)	5 (10)	0 (0)	0.065
Other (%)	6 (12)	3 (8)	0.73
Post transplant			
Mean follow-up time, yr (range)	3.2 (0.5–9.1)	2.7 (0.4–9.3)	0.33
No. of PFTs (SD)	27 (15)	22 (14)	0.9
No. of PFTs with SUPRA pattern	6	0	—
No. of FOBs (SD)	9 (4)	10(6)	1.0
Flow volume loops at 1–6 mo			
FVC, L (SD)	2.30 (0.8)	2.64 (1.0)	0.028
FVC, % predicted (SD)	63.2 (20)	69.8 (21)	0.15
FEV_1, L (SD)	2.18 (0.8)	2.04 (0.9)	0.45
FEV_1, % predicted (SD)	70.3 (25)	64.2 (25)	0.27
FEV_1/FVC ratio (SD)	0.946 (0.05)	0.758 (0.15)	<0.001
Tau*	0.31 (0.10)	0.75 (0.50)	<0.001
Tau**	0.24 (0.10)	0.73 (0.49)	<0.001
Slope	4.45 (0.14)	1.63 (0.16)	<0.001
Vemax, L/s (SD)	7.0 (2.2)	5.3 (2.7)	<0.001
Ve75, L/s (SD)	6.2 (1.9)	3.6 (1.8)	<0.001
Ve50, L/s (SD)	4.9 (1.3)	2.1 (1.1)	<0.001
Ve25, L/s (SD)	2.4 (1.2)	1.0 (0.7)	<0.001
Vemax/FVC, s^{-1} (SD)	3.2 (0.8)	1.9 (0.7)	<0.001
Ve75/FVC, s^{-1} (SD)	2.9 (0.8)	1.4 (0.6)	<0.001
Ve50/FVC, s^{-1} (SD)	2.2 (0.6)	0.8 (0.3)	<0.001
Ve25/FVC, s^{-1} (SD)	1.1 (0.6)	0.4 (0.3)	<0.001
Vi50, L/s (SD)	3.4 (1.2)	4.1 (1.6)	0.014
Vi50/FVC, s^{-1} (SD)	1.63 (0.56)	1.62 (0.46)	0.89
Ve50:Vi50 (SD)	1.58 (0.58)	0.53 (0.19)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; FOB = fiberoptic bronchoscopy; HLT = heart–lung transplant; PFT = pulmonary function test; SUPRA = supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern; Ve = expiratory flow; Vi = inspiratory flow.

Tau* = $-1/\ln[1 - FEV_1/FVC]$, Tau** = $FVC/[2 \times Ve50]$ and slope = $(Ve50/[0.5 \times FVC])$ (8).

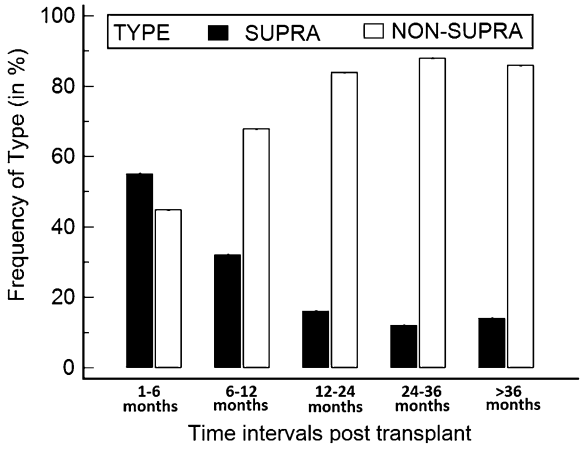

Figure 2. Occurrence of the supranormal expiratory flow and pseudo-variable extrathoracic obstruction (SUPRA) pattern according to time interval.

remained higher in the SUPRA cohort at all time points ($P < 0.01$; Figures 3A and 3B, Table E3). Because the FVCs were higher in the NON-SUPRA cohort we normalized maximal expiratory and inspiratory flows by expressing them as a fraction of FVC. At 1 to 6 months normalized expiratory airflows were 1.6 to 2.9 times and the mean estimated slope was 2.7 times higher in the SUPRA compared with the NON-SUPRA cohort ($P < 0.001$; Table 2, Figure 3B). Normalized inspiratory flows did not differ between the SUPRA and NON-SUPRA cohorts at any time point ($P > 0.1$ for all comparisons; Table E4). As the selection of FVL according to time intervals might not allow comparison of the best expiratory flows in each patient, we also analyzed all Best-FVLs. The Best-FVLs in the SUPRA patients demonstrated significantly higher expiratory flows in all parameters in comparison with NON-SUPRA patients (FEV_1/FVC ratio: 0.967 ± 0.04 vs. 0.862 ± 0.07; Ve50/FVC ratio: 2.5 ± 0.8 s^{-1} vs. 1.2 ± 0.4 s^{-1}; Tau*: 0.27 ± 0.1 and 0.51 ± 0.4; and Tau**: 0.21 ± 0.1 and 0.48 ± 0.4, $P <$ 0.001 for all).

Helium dilution lung volume measurements were available in 9 of 50 patients (18%) in the SUPRA cohort and 8 of 39 patients (20%) in the NON-SUPRA cohort (Table 3, online supplement). The SUPRA cohort demonstrated mild to moderate restriction (TLC 66 ± 13% of predicted). The mean SUPRA vital capacity was decreased to 45 ± 16% of predicted. The mean residual volume (RV) was increased to 112 ± 44% of predicted. The RV/TLC ratio was elevated to 54 ± 14% (vs. 33 ± 5% predicted) in the SUPRA patients. The NON-SUPRA cohort also demonstrated mild restriction (TLC 72 ± 12% of predicted), but the RV/TLC ratio was not elevated (37 ± 6% vs. 34% predicted).

Donor and Recipient Characteristics

Complete demographic information was available for 75 recipient and corresponding donor pairs (Tables 4 and 5). Donors for SUPRA and NON-SUPRA patients did not differ in their mean height (1.69 ± 0.10 m vs. 1.70 ± 0.10 m, $P = 0.7$) and mean pTLC (6.03 ± 1.14 L vs. 6.17 ± 1.14 L, $P = 0.6$). However, donors tended to be younger in the SUPRA cohort (38.6 ± 13.9 yr vs. 45.2 ± 14.4 yr, $P = 0.072$). SUPRA recipients were shorter than NON-SUPRA recipients (1.64 ± 0.08 m vs. 1.72 ± 0.08 m, $P = 0.0014$) and had a lower pTLC (5.49 ± 1.0 1 L vs. 6.25 ± 1.01 L, $P = 0.0019$; Figure 4A). On average the donor lungs in the SUPRA cohort had a pTLC that exceeded the recipients' pTLC by +0.58 L (95% confidence interval [CI], +0.29 to +0.88), whereas in the NON-SUPRA patients, pTLC of donors and recipients were more closely matched (−0.09 L; 95% CI, −0.38 to +0.21). The pTLC ratio was 1.11 (95% CI, 1.06–1.17) in the SUPRA and 0.99 (95% CI, 0.94–1.04) in the

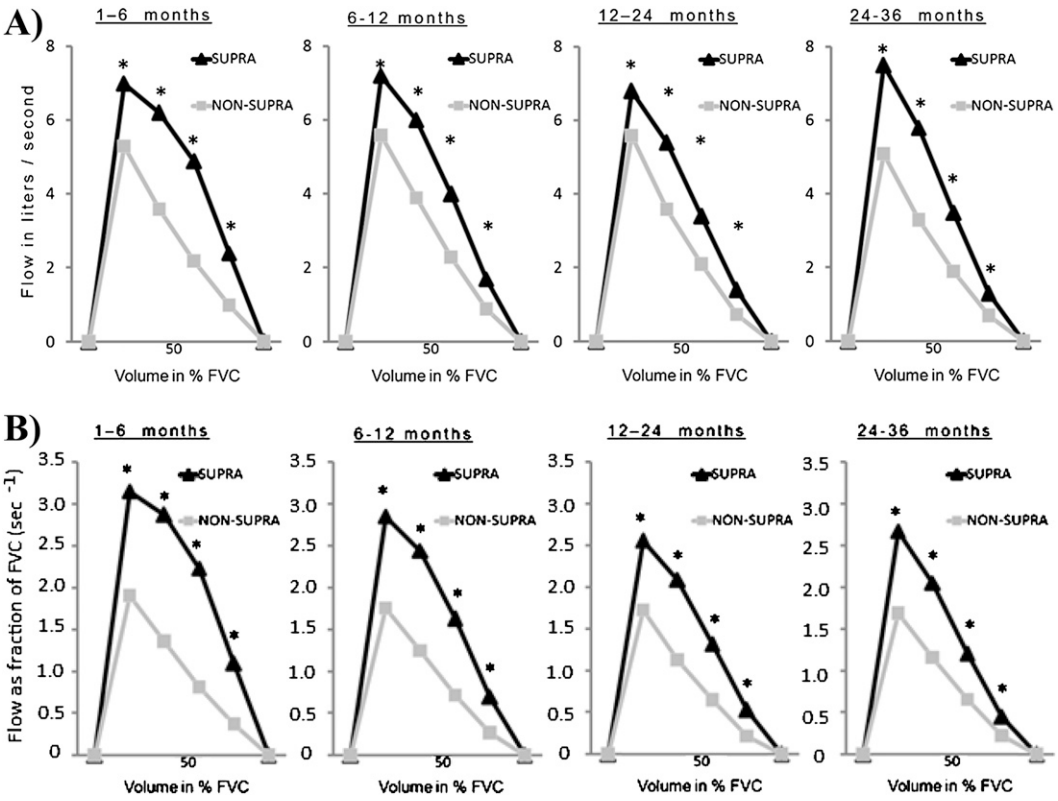

Figure 3. Schematic flow volume loops (FVLs) derived from the mean data of 89 bilateral lung transplant/heart–lung transplant patients according to FVL pattern cohort (supranormal expiratory flow and pseudo-variable extrathoracic obstruction [SUPRA], NON-SUPRA). (*A*) Flow expressed in liters per second. (*B*) Flow expressed as a fraction of FVC (in s^{-1}). *Indicates a significant difference between SUPRA and NON-SUPRA cohort by one-way analysis of variance ($P < 0.05$). Corresponding table is Table E3. Sec = seconds.

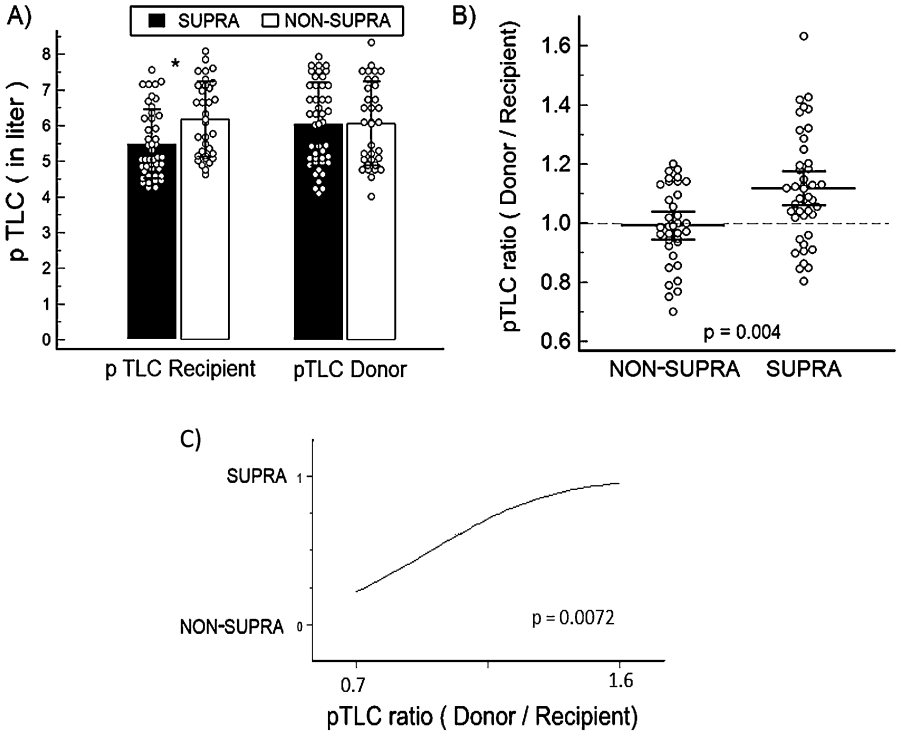

Figure 4. Size mismatch between larger donor lungs and smaller recipient thorax as a predictor of the supranormal expiratory flow and pseudo-variable extrathoracic obstruction (SUPRA) pattern. (*A*) Predicted total lung capacity (pTLC) for recipients and donors in the SUPRA and NON-SUPRA cohort. *Indicates a significant difference between SUPRA and NON-SUPRA cohort by one-way analysis of variance ($P < 0.05$). (*B*) Lung size mismatch expressed as the pTLC ratio (pTLC Donor/pTLC Recipient) in SUPRA and NON-SUPRA cohorts (comparison by one-way analysis of variance). The *solid horizontal lines* represent mean and 95% confidence interval of the mean. The *dashed line* represents exact matching of donor and recipient (pTLC ratio of 1.0). (*C*) Logistic regression analysis showed a significant correlation between a high pTLC ratio and the probability of the SUPRA pattern ($P = 0.0072$).

NON-SUPRA cohort ($P = 0.004$; Figure 4B). Logistic regression analysis showed a significant correlation between a high pTLC ratio and the probability of the SUPRA pattern ($P = 0.0072$; Figure 4C). No other factor besides height mismatch ($P = 0.0024$) was associated with the SUPRA pattern.

Airway Dimension Analysis

There were 10 patients in the SUPRA and 5 patients in the NON-SUPRA cohort who qualified for airway dimension analysis from thoracic high-resolution computed tomography scans (HRCTs) (*see* online supplement). On average, 24 ± 4 individual airways were measurable per patient (range 5.6–496.2 mm^2 in area). To compare airway luminal area measurements, we calculated the average of the individual airway luminal areas within each cohort (Table 6, Table E6). The SUPRA patients had significantly larger transplanted airways compared with the NON-SUPRA patients ($P = 0.009$). This was true for lobar and larger (e.g., bronchus intermedius, $P = 0.03$) and segmental airways, but the difference for segmental airways did not reach significance ($P = 0.09$). Because some airway measurements were not available in some patients, we reanalyzed the comparisons including only airway measurements available in at least 80% of patients in both cohorts. This allowed comparisons of 12 instead of 26 airways (marked by ** in Table E6). The airways in the SUPRA cohort remained significantly larger ($P < 0.05$). The cohorts differed in height (SUPRA 1.68 ± 0.08 m vs. NON-SUPRA 1.73 ± 0.07 m, $P = 0.29$) and in native airway size. We adjusted the airway measurements by dividing each individual airway luminal area by the height of the patient. We also adjusted the airway sizes by dividing each transplanted airway luminal area by the recipient's native tracheal luminal area. After both corrections, the difference between groups became greater (Table 6). After adjustments, the average airway luminal area was 51 to 54% larger in the SUPRA compared with the NON-SUPRA cohort ($P = 0.0003$). Two patients in the SUPRA cohort were transplanted for pulmonary vascular causes and had no significant airways disease. In these patients

TABLE 3. SPIROMETRY AND CORRESPONDING HELIUM DILUTION LUNG VOLUME MEASUREMENTS

	SUPRA (*n* = 9)			NON-SUPRA (*n* = 8)		
Measure Time, mo	13.3 ± 13			19.6 ± 11		
Parameter	Actual (SD)	Pred. (SD)	% Pred. (SD)	Actual (SD)	Pred. (SD)	% Pred. (SD)
Spirometry						
FVC	1.8 (0.8)	3.6 (0.8)	49.0 (15.4)	2.9 (0.9)	4.2 (0.8)	68.4 (14.6)
FEV_1	1.49 (0.9)	2.9 (2.9)	48.6 (18.9)	1.8 (0.7)	3.4 (0.7)	52.4 (14.8)
FEV_1/FVC	81.6 (13.6)	83.0 (2.2)		62.5 (13.2)	81.2 (1.4)	
Helium dilution						
TLC	3.5 (1.0)	5.2 (0.8)	65.6 (12.9)	4.5 (1.1)	6.3 (1.3)	71.6 (12.1)
VC	1.65 (0.8)	3.3 (0.6)	45.2 (16.3)	2.9 (0.9)	4.2 (0.8)	68.4 (15.2)
FRC	2.4 (0.4)	2.9 (0.4)	81.1 (22.2)	2.6 (0.5)	3.6 (0.8)	71.9 (7.8)
RV	1.85 (0.7)	1.7 (0.1)	112.3 (44.0)	1.6 (0.4)	2.1 (0.4)	77.5 (16.1)
RV/TLC	53.7 (14)	32.5 (5.0)		37.1 (6.8)	34.1 (1.8)	

Definition of abbreviations: pred. = predicted; RV = residual volume; SUPRA = supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern.

TABLE 4. DONOR AND RECIPIENT CHARACTERISTICS IN THE SUPRANORMAL EXPIRATORY FLOW AND PSEUDO-VARIABLE EXTRATHORACIC OBSTRUCTION PATTERN COHORT

Characteristic Parameter	SUPRA ($n = 41$) Recipient	Donor	Mismatch	*P* Value
Age, yr (SD)	44.2 (14.8)	38.6 (13.9)	−6.9 (18)	<0.03
Height, m (SD)	1.64 (0.08)	1.69 (0.11)	+0.05 (0.09)	<0.002
Weight, kg (SD)	59.3 (13)	77.5 (20.4)	+17.9 (24)	<0.001
BMI (SD)	21.8 (4.3)	27.6 (7.5)	+5.2 (8)	<0.001
pTLC, L (SD)	5.49 (1.0)	6.03 (1.1)	+0.58 (0.81)	<0.0004
pTLC ratio (95% CI)			1.11 (1.06–1.18)*	

Definition of abbreviations: BMI = body mass index; CI = confidence interval; pTLC = predicted total lung capacity; SUPRA = supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern.

pTLC of each donor and recipient was calculated using the regression equations recommended by the American Thoracic Society/European Respiratory Society (9). Comparisons of donors and recipients within each cohort were made with a Student *t* test.

* Comparison of pTLC ratio SUPRA vs. NON-SUPRA cohort by one-way analysis of variance: $P = 0.004$.

TABLE 5. DONOR AND RECIPIENT CHARACTERISTICS IN THE NON–SUPRANORMAL EXPIRATORY FLOW AND PSEUDO-VARIABLE EXTRATHORACIC OBSTRUCTION PATTERN COHORT

Characteristic Parameter	NON-SUPRA ($n = 34$) Recipient	Donor	XMismatch	*P* Value
Age, yr (SD)	44.4 (14.1)	45.2 (14.4)	0.3 (17)	0.92
Height, m (SD)	1.72 (0.10)	1.70 (0.10)	−0.02 (0.1)	0.13
Weight, kg (SD)	62.8 (12.1)	79.0 (22.5)	+15.5 (24)	<0.001
BMI (SD)	21.5 (3.5)	27.7 (7.2)	+6.1 (8)	<0.001
pTLC, L (SD)	6.25 (1.01)	6.17 (1.14)	−0.09 (0.8)	0.55
pTLC ratio (95% CI)			0.99 (0.94–1.04)*	

For definition of abbreviations see Table 4.

pTLC of each donor and recipient was calculated using the regression equations recommended by the American Thoracic Society/European Respiratory Society (9). Comparisons of donors and recipients within each cohort were made with a Student *t* test.

* Comparison of pTLC ratio SUPRA vs. NON-SUPRA cohort by one-way analysis of variance: $P = 0.004$.

we compared airway luminal area measurements from CT scans before and after transplantation. The average luminal area was 32% larger on the post-transplant CT in one ($P = 0.02$) and 19% larger in the other patient ($P = 0.06$) (Tables E7 and E8).

Clinical Outcomes

The mean follow-up time was 3.0 years (range 0.4–9.3 yr), and 30 deaths occurred (Table 7). The most common causes of death were BOS (37%), BOS complicated by infection (26%), infection (13%), and malignancy (10%). In the SUPRA cohort, with a mean follow-up of 3.2 years (range 0.5–9.1 yr), 11 deaths occurred. In the NON-SUPRA cohort, with a mean follow up of 2.7 years (range 0.4–9.3 yr), 19 deaths occurred. The SUPRA pattern was associated with a significantly better survival ($P = 0.009$; Figure 5A). Estimated 5-year survival rates were 70% in the SUPRA and 28% in the NON-SUPRA cohort. The SUPRA and NON-SUPRA cohorts did not differ significantly regarding causes of mortality, occurrence of BOS, or acute rejection. However, airway complications were more common in the NON-SUPRA cohort (12 vs. 41%, $P = 0.0026$). In univariable Cox proportional hazard regression models the presence of BOS ($P = 0.003$), the presence of the SUPRA pattern ($P = 0.014$), Ve50 ($P = 0.03$), and Ve50/FVC ($P = 0.03$) were associated with survival (Table 8). Acute rejection, airway complications, transplant indications, recipient and donor age, and pTLC ratio were not associated with survival. To examine the effect of the SUPRA pattern on survival in the context of BOS we constructed a multivariable Cox proportional hazard regression model. The SUPRA pattern remained associated with better survival (relative risk, 0.41; 95% CI, 0.21–0.93; $P = 0.033$; Table 8). Although the occurrence of BOS did not differ significantly between SUPRA and NON-SUPRA cohorts ($P = 0.1$), mean time from transplant to BOS diagnosis was longer in SUPRA patients (1.89 ± 0.85 yr vs. 0.97 ± 0.71 yr, $P = 0.003$). At all time points SUPRA patients were more likely to be BOS free ($P = 0.01$; Figure 5B). SUPRA patients diagnosed with BOS had a trend toward better survival compared with NON-SUPRA patients with BOS ($P = 0.08$).

The SUPRA FVL Pattern in the Inova Fairfax Hospital Cohort

There were 43 patients who had at least two FVLs available for review (*see* online supplemental information and Table E10). The SUPRA FVL pattern occurred in 49% of patients. The mean follow-up was 3.8 years, and 14 deaths occurred. Five deaths occurred in the SUPRA and 9 deaths in the NON-SUPRA cohort. There was a trend toward better survival of the SUPRA cohort ($P = 0.12$).

DISCUSSION

In this report we describe the SUPRA FVL pattern in a cohort of BLT and HLT patients. The SUPRA FVL pattern is common, occurring in more than 50% of patients, and its presence is associated with improved survival. Contrary to our initial hypothesis, the pTLC of donor lungs was generally larger than recipient pTLC, which was associated with lower FVCs and higher expiratory flow capacities. CT airway dimension analysis showed significantly larger airway luminal areas in SUPRA patients compared with NON-SUPRA patients.

Physiology of the SUPRA FVL Pattern

The key feature of the SUPRA FVL pattern is the supranormal expiratory flow. At 1 to 6 months after transplantation, the FEV_1/FVC ratio was 0.964 ± 0.05. The Ve50/FVC ratio in the SUPRA cohort was 2.8 times greater than in the NON-SUPRA cohort and 2.2 times greater than would be predicted for the SUPRA FVC (13). Further key characteristics of the SUPRA pattern were lower FVCs and a high RV/TLC ratio. Each of these features could be explained by the observed mismatch between relatively larger donor lungs transplanted into a recipient with a smaller pTLC. A theoretical model of lung volume changes caused by lungs that are larger in relation to the size of the thorax predicted a high RV/TLC ratio (14). A similar pattern of an elevated RV/TLC ratio was reported in seven HLT patients who had received significantly larger donor lungs (mean pTLC ratio 1.30), for whom 1 year after transplant the RV was in the predicted range for the (larger) donor lungs, whereas TLC was in the predicted range for the recipient (15). In younger individuals RV is determined by chest wall mechanics and not airway closure (16). The age of donor lungs and the terminal slope of FVLs in the SUPRA cohort suggest that RV is determined by recipient chest wall mechanics or termination of effort. The elevated RV/TLC ratio and decreased TLC may also explain the lower FVCs in the SUPRA cohort. Thus, the supranormal expiratory flow capacity in SUPRA patients could be a result of the lung size mismatch.

Size Mismatch Could Cause High Expiratory Flow

A mismatch between relatively larger donor lungs transplanted into a smaller thorax could affect airway resistance because of dysanapsis. This term was used by Green and colleagues to

TABLE 6. AIRWAY DIMENSIONS BY THORACIC HIGH-RESOLUTION COMPUTED TOMOGRAPHY SCANS

	Absolute Area (mm^2)		Height corr. Area (mm^2/m)*		% of Tracheal Area†		No. of Patients	
	SUPRA	NON- SUPRA	SUPRA	NON- SUPRA	SUPRA	NON- SUPRA	SUPRA	NON- SUPRA
Native airways (trachea)	307	353	183	204	N/A	N/A	10	5
P value (native)	0.2		0.37		N/A			
Lobar and larger airways	90.6	64.0	53.6	31.0	31.0	17.4	8.9	3.5
P value (lobar and larger)‡	0.03		0.005		0.003			
Segmental airways	32.4	28.6	19.2	14.5	11.1	8.1	7.8	3.5
P value (segmental)§	0.09		0.005		0.006			
Combined (lobar/larger and segmental) airways	48.1	39.2	28.5	18.9	16.4	10.6	8.1	3.5
P value (combined)‖	0.009		0.0003		0.0003			

Definition of abbreviations: corr. = corrected; N/A = not applicable; SUPRA = supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern. Table E6 provides details on individual airway luminal area measurements. Figure E2 shows an airway tree diagram with assigned labels of airway segments.

* Correction for height by dividing each individual airway luminal area by the height of the individual recipient.

† Correction by expressing each transplanted airway luminal area as a fraction of each recipient's native tracheal luminal area.

‡ Comparison of the all individual lobar and larger airway diameters between SUPRA and NON-SUPRA cohort.

§ Comparison of all individual segmental conductive airway diameters between SUPRA and NON-SUPRA cohort.

‖ Comparison of all individual lobar/larger and segmental conductive airway diameters between SUPRA and NON-SUPRA cohort.

describe a size mismatch between airways relative to an individual's lung and thorax volume (13). Green and colleagues found a correlation between the interindividual variability in the expiratory FVL and the structure of the larger airways (13). Mead quantified dysanapsis by the ratio of a measurement known to be sensitive to airway size (Ve50) to a measurement of lung size (FVC) (17). The normal range of the Ve50/FVC ratio is 1.0 to 1.3 s^{-1} (12). In the SUPRA cohort the Ve50/FVC ratio at 1 to 6 months post-transplant was 2.23 ± 0.6 s^{-1} (vs. 0.82 ± 0.34 s^{-1} in NON-SUPRA cohort). Our analysis of airway dimensions on HRCT scans showed significantly larger transplanted airways in SUPRA compared with NON-SUPRA patients ($P = 0.009$). The difference in airway dimensions between the cohorts and the corresponding differences in expiratory flow capacity suggests that the structure of transplanted airways is important for post-transplant lung function. Furthermore an HRCT study of patients with moderate asthma demonstrated a significant correlation between the diameter of larger airways, the FEV_1/FVC ratio, and airway hyperresponsiveness (18). An association between transplanted lungs that were smaller than the recipient's thorax and airway hyperresponsiveness was reported in a cohort of lung transplant patients (19).

Elastic recoil could also be affected by lung size mismatch. Decreased elastic recoil might be predicted from transplanting larger donor lungs into a smaller recipient thorax (13). However, changes in surface tension could counteract this effect and lead to an overall increase in elastic recoil (20). Chest wall strapping, a situation conceptually similar to a size mismatch of a relatively larger lung in relation to a restricted thorax, causes increased elastic recoil of the lungs (21–23). In eight normal males, chest wall strapping caused a reduction of VC and FRC by about 40%, whereas RV decreased by only 11% (22). Elastic recoil was increased by 64%. This was associated with an increase in Ve50 by 88% and an increase in the Ve50/VC ratio by 302% (22). Increased recoil pressure from limiting full inspiration and breathing close to RV is best explained by changes in surface tension (22, 24). This effect seems to persist over time and is not related to atelectasis (25). Breathing close to RV and limited inspiration would be expected from transplantation of lungs that are larger than a recipient's thorax. This could also cause increased elastic recoil, which is a critical determinant of maximum expiratory flow (6). Chacon and colleagues analyzed respiratory mechanics in 15 BLT/HLT patients with a mean pTLC ratio of 1.09 and found the elastic recoil of the transplanted lungs to be mildly increased (26). Increases in elastic recoil and higher expiratory flow rates have also been described for limitations of inspiration caused by pleural effusions and pneumothorax (27). The frequency of pleural pathology in our cohort was high, but there was no difference in frequency between SUPRA and NON-SUPRA cohorts (*see* online supplement).

The SUPRA FVL Pattern and Survival

The SUPRA FVL pattern was associated with significantly better survival ($P < 0.009$; Figure 5A). The leading cause of long-term mortality after lung transplantation is BOS, which is believed to be due to chronic allograft rejection (8, 28). BOS has a prevalence of about 70% at 5 years and is characterized by a progressively worsening obstructive ventilatory defect (28). Although the overall occurrence of BOS did not differ significantly between SUPRA and NON-SUPRA cohorts, time to BOS diagnosis was longer in the SUPRA cohort, and at all time points SUPRA patients were less likely to have BOS (Figure 5B). Furthermore, higher expiratory flows in the SUPRA cohort in the first 6 to 12 months after transplantation could have provided a reserve that resulted in improved survival in patients subsequently affected by BOS. Indeed we found a trend toward better survival in SUPRA patients affected by BOS in comparison to NON-SUPRA patients with BOS.

TABLE 7. THE SUPRANORMAL EXPIRATORY FLOW AND PSEUDO-VARIABLE EXTRATHORACIC OBSTRUCTION FLOW VOLUME LOOP PATTERN AND CLINICAL OUTCOMES IN THE JOHNS HOPKINS HOSPITAL COHORT

Clinical Outcome	SUPRA	NON-SUPRA	*P* Value
No.	50	39	
Mean follow-up, yr (range)	3.2 (0.5–9.2)	2.7 (0.4–9.3)	0.33
Airway complications (%)	6 (12)	16 (41)	0.0026
Acute rejection (%)	17 (34)	16 (41)	0.76
Diagnosis of BOS (%)	13 (26)	17 (43)	0.1
Time to BOS diagnosis, yr (SD)	1.89 (0.85)	0.97 (0.70)	0.003
Patients with BOS alive	7 (54)	5 (29)	0.08
Dead at last follow-up (%)	11 (22)	19 (49)	0.0125
Causes of mortality (%)			
BOS	3 (27)	8 (42)	0.053
Infection	1 (9)	3 (16)	0.32
BOS + infection	4 (36)	4 (21)	0.73
Malignancy	1 (9)	2 (11)	0.58
Other	2 (18)	2 (11)	1.0

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; SUPRA = supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern.

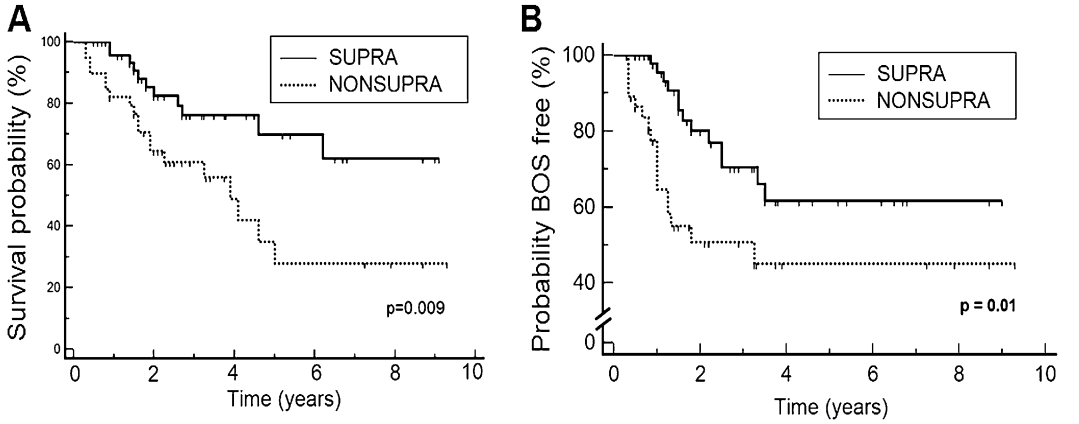

Figure 5. The supranormal expiratory flow and pseudo-variable extrathoracic obstruction (SUPRA) pattern is associated with clinical outcomes. (*A*) Kaplan-Meier survival estimates for patients in SUPRA and NON-SUPRA flow-volume loop patients in the Johns Hopkins Hospital cohort. (*B*) Kaplan-Meier estimates for the probability of being free of bronchiolitis obliterans syndrome (BOS).

Decreased surfactant protein levels have been reported after lung transplantation, and this was associated with onset of BOS after transplantation (29, 30). In models of decreased lung compliance, increases in surfactant protein and phospholipid content occurred (31, 32). Changes in surfactant resulting from transplantation of a larger lung to a smaller recipient thorax could have implications for the timing and occurrence of BOS. Several investigators have reported clinical outcomes after lung transplantation with donor–recipient size mismatches. No association with clinical outcomes was found, except in the investigation that included the largest number of patients (33–36). This study of 520 BLT/single lung transplant patients showed worse survival with transplanting smaller donor lungs in relation to the recipient thorax (36). We found no significant association between the pTLC ratio and survival. Using pTLC to estimate the relationship between donor lungs to recipient (post-transplant) thorax appears to be imprecise.

TABLE 8. COX PROPORTIONAL HAZARDS MODELS OF RISK FACTORS FOR DEATH

Risk Factor	RR	95% CI	*P* Value
Univariable			
Recipient age (per yr)	0.98	0.95–1.01	0.26
Donor age (per yr)	1.03	0.99–1.07	0.15
pTLC ratio	0.33	0.04–2.52	0.28
pTLC ratio > 1.0	0.73	0.35–1.56	0.42
Transplant indications			
Cystic fibrosis	1.47	0.67–3.22	0.33
COPD	1.07	0.46–2.50	0.88
Congenital heart disease	—	—	0.96
Interstitial lung disease	1.43	0.54–3.79	0.47
Pulmonary hypertension	0.88	0.30–2.53	0.81
Sarcoidosis	0.63	0.15–2.69	0.54
Other	0.71	0.22–2.34	0.57
Occurrence of acute rejection	1.27	0.63–2.63	0.49
Occurrence of airway complication	1.52	0.71–3.24	0.28
Occurrence of BOS	3.06	1.47–6.37	0.003
Presence of SUPRA pattern	0.38	0.18–0.81	0.01
Flow volume loops (1–(6 mo)			
Ve50	0.78	0.62–0.97	0.03
Ve50/FVC	0.59	0.36–0.95	0.03
Ve50:Vi50	0.73	0.40–1.33	0.30
Multivariable			
Occurrence of BOS	2.75	1.30–5.81	0.008
Presence of SUPRA pattern	0.44	0.21–0.93	0.03

Definition of abbreviations: BOS = bronchiolitis obliterans syndrome; COPD = chronic obstructive pulmonary disease; pTLC = predicted total lung capacity; SUPRA = supranormal expiratory flow and pseudo-variable extrathoracic obstruction pattern; Ve = expiratory flow; Vi = inspiratory flow.

Model chi-square = 13.6, $P < 0.001$.

It is unclear if increased elastic recoil or larger airways is the predominant factor causing the supranormal expiratory flow. If larger airways is the key factor, then a direct airway assessment of airway anatomy of potential donors could be part of the donor evaluation process. If increased elastic recoil is the predominant factor, then surgical strategies to manipulate the recipient thorax size (i.e., plombage) could be considered. Furthermore, the hypothesis of surfactant changes after transplantation in relation to size mismatch and its association with BOS should be investigated, as this could inform studies of surfactant replacement strategies after lung transplantation (37, 38).

Our investigation has several limitations. It is a primarily a single-center study and retrospective in its design. However our findings are supported and validated by review of FVLs in an independent BLT/HLT cohort from another program. We have no data on elastic recoil to support our hypothesis of increased elastic recoil in the SUPRA cohort. We demonstrated a significant relationship between lung size mismatch and the presence of the SUPRA pattern, but there was substantial overlap in the ranges of the pTLC ratio between SUPRA and NON-SUPRA patients. The helium lung volume measurements showing an elevated RV/TLC ratio and the HRCT analysis demonstrating larger airways in SUPRA patients are limited by the small number of patients analyzed in each cohort and the clinical indication for these studies. The quality of the CT scans allowed us to only analyze airways up to the segmental bronchi. It remains unclear how smaller airways or changes in the chest wall mechanics over time might contribute to the physiology of the SUPRA FVL pattern.

Conclusions

We defined the SUPRA FVL pattern and found that it is common, especially in the early post-transplant period. The key feature of the SUPRA FVL pattern is the supranormal expiratory flow. Restriction of donor lungs in a relatively smaller recipient thorax could cause the SUPRA FVL pattern. Increased elastic recoil from limitations on inspiration and lower airway resistance from larger transplanted airways may explain the supranormal expiratory flow. The association with improved survival deserves further investigation, which could lead to new therapeutic strategies to improve clinical outcomes in lung transplant patients.

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