Noninvasive investigations for the early detection of chronic airways dysfunction following lung transplantation

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BACKGROUND: The diagnosis of chronic rejection after lung transplantation is limited by the lack of a reliable test to detect airways disease early.
OBJECTIVES: To determine whether maximum midexpiratory flow (MMEF), or changes on high resolution computed tomography (HRCT) or ventilation/perfusion lung (V/Q) scans are sensitive and specific for early detection of bronchiolitis obliterans syndrome (BOS; forced expiratory volume in 1 s [FEV_1] less than 80% post-transplant baseline) by evaluating long term survivors of lung transplantation at two sequential time points.
METHODS: Twenty-two stable lung transplant recipients underwent spirometry, HRCT scanning and V/Q scanning 1.6±0.9 years and 3.1±1.1 years post-transplant (time points 1 and 2, respectively; mean ± SD).
RESULTS: Although HRCT was sensitive for the detection of BOS, it lacked specificity, and hence, there were no significant relationships between the presence of BOS and any of the HRCT parameters evaluated at time 1 or time 2. Of the V/Q parameters studied, the presence of heterogeneous perfusion (P=0.04, sensitivity 100%, specificity 33%) and segmental perfusion defects (P=0.04, sensitivity 60%, specificity 83%) were significantly related to BOS, but only at time 2. MMEF less than or equal to 75% post-transplant baseline was significantly related to the presence BOS at time 1 only (P=0.05, sensitivity 100%, specificity 47%). MMEF less than or equal to 75% post-transplant baseline at time 1 was sensitive for the development of BOS at time 2, but was limited by low specificity.
CONCLUSIONS: In this group of lung transplant recipients, HRCT and V/Q scanning, as well as analysis of MMEF, did not add information that was clinically more useful than FEV_1 for the early identification of chronic rejection.

Key Words: *Bronchiolitis obliterans syndrome; High resolution computed tomography; Lung transplantation; Spirometry; Ventilation/perfusion scans*

Examens non effractifs pour la détection précoce du dysfonctionnement chronique des voies aériennes après une greffe pulmonaire

CONTEXTE : L'absence de tests fiables permettant de déceler tôt une atteinte des voies aériennes limite la pose du diagnostic de rejet chronique après une greffe pulmonaire.
OBJECTIF : Vérifier, en deux moments séquentiels (T_1 et T_2), si le débit maximal expiratoire médian (DMEM) ou des modifications de la tomodensitométrie haute résolution (TDM-HR) ou de la scintigraphie de ventilation et de perfusion (V/Q) se montrent suffisamment sensibles et spécifiques pour la détection précoce du syndrome de bronchiolite oblitérante (SBO; volume expiratoire maximal par seconde [VEMS]) inférieur à 80 %, au départ, après la transplantation) chez des patients porteurs, depuis assez longtemps, d'une greffe pulmonaire.
MÉTHODE : Vingt-deux greffés du poumon, dans un état stable, ont été soumis à une spirométrie, à une TDM-HR et à une scintigraphie V/Q 1,6 ± 0,9 an et 3,1 ± 1,1 ans après la transplantation (T_1 et T_2 respectivement; moyenne ± écart-type).
RÉSULTATS : Même si la TDM-HR s'est montrée suffisamment sensible pour la détection du SBO, elle manquait de spécificité; aussi n'a-t-il pas été possible d'établir de liens importants entre le SBO et l'un ou l'autre des paramètres évalués par TDM-HR en T_1 et T_2. Parmi les paramètres liés au rapport V/Q, les images de perfusion hétérogène (P = 0,04; sensibilité : 100 %; spécificité : 33 %) et de perfusion segmentaire (P = 0,04; sensibilité : 60 %; spécificité : 83 %) se sont révélées en assez étroite relation avec le SBO, mais en T_2 seulement. Un DMEM égal ou inférieur à 75 % de la valeur de départ après la transplantation était significativement lié à la présence du SBO mais en T_1 seulement (P = 0,05; sensibilité : 100 %; spécificité : 47 %). Ce dernier paramètre était certes sensible pour déceler la présence du SBO en T_2, mais il manquait de spécificité.
CONCLUSION : Les examens effectués dans le présent groupe de greffés du poumon, soit la TDM-HR et la scintigraphie V/Q, de même que l'analyse du DMEM, n'ont rien apporté de plus sur le plan clinique que le VEMS pour la détection précoce du rejet chronique.

Lung transplantation has become an accepted form of therapy for certain carefully selected patients with advanced cardiorespiratory disease (1). Unfortunately, long term survival is limited by obliterative bronchiolitis (OB), which is thought to be a manifestation of chronic rejection and affects up to 50% of long term survivors by three years post-transplantation (2). The early identification of chronic rejection following lung transplantation is problematic due to the lack of a reliable

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diagnostic test. Transbronchial biopsy diagnosis of OB has a low sensitivity (3,4), and therefore, the diagnosis of chronic airways rejection is generally based on changes in pulmonary function (5). The commonly used definition of chronic airways rejection, bronchiolitis obliterans syndrome (BOS), is defined as a decline in the forced expiratory volume in 1 s (FEV_1) of more than 20% from the post-transplant baseline in the absence of acute rejection or active infection (5).

Once BOS is identified, alterations in immunosuppression generally provide, at best, only modest benefit (6), presumably because the immunopathological process is already well established. This reinforces the need to identify a more reliable means of detecting chronic airways rejection, with the hope that earlier diagnosis allows for improved outcomes with therapeutic interventions.

In smokers, the maximal midexpiratory flow from 25% to 75% of vital capacity (MMEF) is known to be a more sensitive early marker of small airways disease than the FEV_1 (7). This finding has also been reported in lung transplant recipients (2,8). The most recent recommendations suggest that a 25% reduction in the MMEF from the post-transplant baseline should raise the question of early BOS, and is now referred to as the "potential BOS stage" or BOS grade "0-p" (5). Certain imaging techniques may also be helpful for early diagnosis of small airways disease. High resolution computed tomography (HRCT) scanning has been shown to be useful for the identification of OB in nontransplant patients (9-11). Several HRCT abnormalities have also been found in patients with transplant-related OB (12-15). Finally, abnormalities on ventilation-perfusion (V/Q) scans have also been shown to be present in chronic airways rejection in lung transplant recipients (16).

The aim of this pilot study was to evaluate spirometry, HRCT scan and V/Q scan results at two separate times at least one year apart to determine whether MMEF, HRCT and V/Q scanning are early predictors of BOS in long term survivors of lung transplantation. The presence or absence of BOS according to changes in the FEV_1 was defined as the gold standard for comparison in this study.

PATIENTS AND METHODS

This was a retrospective review of the annual test results from single-lung, double-lung and heart-lung recipients who received transplants at the University of British Columbia, Vancouver, British Columbia, between April 1989 and February 1998, and who had survived at least two years. The test results were taken from routine annual examinations scheduled according to the protocol at the University of British Columbia. Studies were performed for surveillance reasons at a time when patients were expected to be clinically well and were performed within a four-week period. Patients were excluded from the study if they were not free of acute rejection and active pulmonary infection (clinically, bronchoscopically and radiographically) at the time of the two annual examinations. For imaging studies, only those abnormalities identified in transplanted lungs were included for evaluation.

Spirometry

Spirometry was performed according to American Thoracic Society criteria (17) at each clinic visit and at the time of annual follow-up tests. The average of the two highest consecutive post-transplant values was taken to be the post-transplant baseline for FEV_1 and MMEF. Grading of BOS was according to the FEV_1 per cent post-transplant baseline (FEV_1 per cent baseline) as defined by the International Society for Heart and Lung Transplantation (5): grade 0 – FEV_1 less than 80% baseline; grade 1 – FEV_1 65% to 79% baseline; grade 2 – FEV_1 50% to 64% baseline; and grade 3 – FEV_1 less than 50% baseline. The tests were performed in the pulmonary function laboratory using Sensormedics (Anaheim, USA) spirometers, which were calibrated daily. The MMEF was calculated using the spirometer software.

HRCT

HRCT scans of the chest were performed with a GE 9800 or Hi Speed Advantage (GE Medical Systems, USA) scanner using 1 to 1.5 mm collimation and a high spatial frequency reconstruction algorithm. End-inspiratory scans were obtained at 10 mm intervals, and end-expiratory scans were obtained at three to five equally spaced levels between the aortic arch and 2 cm above the dome of the diaphragm. The images were photographed at optimal windows for assessment of lung parenchyma (window level –700 HU, window width 1000 to 1500 HU).

HRCT scans were evaluated by a radiologist who was unaware of the patient's clinical status, and were scored for the presence of air trapping (ATct), mosaic perfusion (MPct) and bronchial dilation (BDct). ATct was defined as areas of decreased attenuation and perfusion on scans obtained during expiration. MPct was defined as localized areas of reduced parenchymal attenuation and vascularity on HRCT scans obtained during inspiration. BDct was defined by the presence of bronchi with an internal diameter greater than that of the adjacent pulmonary artery.

V/Q scans

Ventilation imaging was performed following the inhalation of 185 to 370 MBq of xenon-133 (Xe-133) using a 20% symmetric window centred on the 80 Kev energy peak. A single breath image was obtained in the posterior projection after the inhalation of Xe-133 followed by a breath hold for 10 s. Equilibrium images were acquired while the patient rebreathed Xe-133 within a closed system for 2 min. Washout images were performed as a 10 s dynamic sequence for 4 min or until there was no activity in the lungs.

After ventilation images were obtained, perfusion imaging was performed following intravenous administration of 100 MBq of technetium 99m (Tc-99m) macroaggregated albumin (MAA) containing 100,000 to 300,000 particles. Tc-99m MAA was injected over five to 10 respiratory cycles with the patient in the supine position. Anterior, posterior, right posterior oblique and left posterior oblique images were acquired for 500,000 counts using a 20% symmetric window centred on the 140 Kev energy peak. All imaging was performed on a large field of view camera equipped with a low energy, all purpose collimator.

V/Q scans were evaluated by a nuclear medicine physician unaware of the patient's diagnosis, and were scored for the presence of air trapping (ATvq), heterogeneous perfusion (HPvq) and segmental perfusion abnormality (SPvq). Clinical information, surgical history and chest radiographs were not provided at the time of image interpretations. ATvq was defined as persistent activity within the lung following 3 min of washout imaging.

TABLE 1
Subject characteristics in a study examining noninvasive investigations for the early detection of chronic airways dysfunction following lung transplantation

Subject	Age (years)	Disease	Sex	Transplant	Time 1 (years post-transplant)	Time 2 (years post-transplant)	Time 2 – Time 1 (years)
1	42	Eisenmenger's	F	HL	1	2	1
2	49	Emphysema	F	SL	1	5	4
3	61	Emphysema	F	SL	1	2	1
4	12	Cystic fibrosis	F	HL	2	3	1
5	45	Emphysema	M	SL	4	5	1
6	57	Emphysema	F	DL	1	2	1
7	59	Emphysema	M	DL	1	2	1
8	58	Emphysema	F	SL	2	3	1
9	42	Primary pulmonary hypertension	F	HL	1	2	1
10	31	Cystic fibrosis	M	DL	1	2	1
11	28	Primary pulmonary hypertension	F	DL	2	3	1
12	48	Emphysema	F	SL	1	2	1
13	56	Idiopathic pulmonary fibrosis	M	SL	1	2	1
14	59	Emphysema	F	SL	2	3	1
15	39	Primary pulmonary hypertension	F	DL	1	2	1
16	47	Emphysema	F	SL	1	3	2
17	46	Eisenmenger's	F	HL	2	5	3
18	50	Emphysema	M	DL	3	4	1
19	50	Emphysema	F	SL	1	4	3
20	42	Emphysema	M	HL	3	4	1
21	61	Emphysema	M	SL	1	4	3
22	36	Bronchiectasis	F	DL	1	3	2
Mean	46	–	–	–	1.55	3.05	1.50
SD	12	–	–	–	0.86	1.09	0.91

SL Single-lung transplant; DL Double-lung transplant; HL Heart-lung transplant

HPvq was defined as nonuniform distribution of Tc-99m MAA without evidence of segmental or subsegmental perfusion defects. SPvq was defined as a wedge-shaped perfusion defect that corresponded with segmental pulmonary anatomy.

Statistical analysis

Variables were correlated using 2×2 analysis separately at each time point, as well as between time 1 and time 2 by means of contingency tables (Pearson's χ^2, $P<0.05$ was significant). Significance in larger tables was localized by calculating standardized deviates (18).

RESULTS

Of the 53 patients who received transplants between April 1989 and February 1996, 30 had survived for at least two years by February 1998. The study population consisted of those 22 patients for whom results were available from two annual tests at a time when they were free of acute rejection and infection. These patients were one to four years (mean ± SD 1.6±0.9 years) post-lung transplantation at the time of the first study point (time 1) and two to five years (mean 3.1±1.1 years) post-transplant at the time of the second study point (time 2). The mean time interval between time 1 and time 2 was 1.5±0.9 years. There were seven male and 15 female patients, whose mean age was 46±12 years (range 12 to 61 years). The underlying lung disease was emphysema in 13 patients (59%), primary pulmonary hypertension (PPH) in three patients (14%), cystic fibrosis in two patients (9%), Eisenmenger's syndrome in two patients (9%), idiopathic pulmonary fibrosis in one patient (5%) and bronchiectasis in one patient (5%). Ten patients (45%) received single-lung transplants, seven (32%) received double-lung transplants and five (23%) were recipients of heart-lung transplants (Table 1). Results of spirometry, HRCT and V/Q scans at time 1 and time 2 are summarized in Tables 2 and 4.

The eight patients excluded from the study did not have complete data available, were lost to follow-up, or had acute rejection or infection at the time of their annual examinations.

Time point 1

At time 1, five of the patients (23%) had BOS. All five patients also had MMEF less than or equal to 75% baseline (Table 3). Table 3 summarizes the relationships at time 1 between BOS (FEV_1 less than 80% baseline) and MMEF less than or equal to 75%, or the presence of any of the HRCT and V/Q abnormalities studied. At time 1, there were no significant relationships between BOS and the presence of any of the HRCT or V/Q parameters evaluated; however, there was a significant relationship between BOS at time 1 and MMEF less than or equal to 75% at time 1 (P=0.05, sensitivity 100%, specificity 47%).

TABLE 2
Spirometry and imaging results at time 1 in a study examining noninvasive investigations for the early detection of chronic airways dysfunction following lung transplantation

Subject	FEV_1 % of post-transplant baseline	MMEF % of post-transplant baseline	HRCT MPct	HRCT BDct	HRCT ATct	V/Q ATvq	V/Q HPvq	V/Q SPvq
1	104	84	–	+	–	–	+	–
2	102	113	–	–	–	–	–	–
3	100	92	–	–	–	–	+	+
4	100	90	+	+	+	–	+	–
5	100	28	+	–	–	–	–	–
6	99	54	+	+	+	–	–	+
7	98	87	–	–	–	–	+	–
8	98	47	–	+	–	–	–	–
9	96	100	+	–	–	–	–	–
10	95	93	–	–	–	–	–	–
11	94	32	+	+	+	–	+	+
12	93	47	–	–	–	+	+	+
13	93	64	+	–	+	+	+	–
14	88	92	–	–	–	–	–	–
15	87	70	+	–	–	+	+	+
16	85	34	+	+	+	–	+	–
17	83	56	–	+	–	+	+	+
18	75	27	+	+	+	–	+	–
19	69	34	–	–	–	–	–	–
20	60	29	+	–	–	–	+	+
21	58	16	+	+	–	+	+	+
22	47	11	+	+	+	+	+	–

– Abnormality absent; + Abnormality present; ATct Air trapping on high resolution computed tomography (HRCT); ATvq Air trapping on ventilation/perfusion scan (V/Q); BDct Bronchial dilation on HRCT; FEV_1 Forced expiratory volume in 1 s; HPvq Heterogeneous perfusion on V/Q; MMEF Maximum midexpiratory flow; MPct Mosaic perfusion on HRCT; SPvq Segmental perfusion defect on V/Q

TABLE 3
Relationships of high resolution computed tomography (HRCT), ventilation/perfusion scan (V/Q) and maximum midexpiratory flow (MMEF) with bronchiolitis obliterans syndrome (BOS) at time 1

BOS at time 1 versus:	P	Sensitivity (%)	Specificity (%)
MMEF≤75% post-transplant baseline	0.05	100	47
MPct	0.19	80	53
BDct	0.46	60	59
ATct	0.66	40	71
ATvq	0.47	40	76
HPvq	0.39	80	41
SPvq	0.85	40	65

ATct Air trapping on HRCT; ATvq Air trapping on V/Q; BDct Bronchial dilation on HRCT; HPvq Heterogeneous perfusion on V/Q; MPct Mosaic perfusion on HRCT; SPvq Segmental perfusion defect on V/Q

Time point 2

At time 2, 10 of the patients (45%) had BOS (Table 4). All 10 patients also had MMEF less than or equal to 75% (Table 5, P not significant, sensitivity 100%, specificity 25%). Table 5 summarizes the relationships at time 2 between BOS and MMEF less than or equal to 75%, or the presence of any of the HRCT and V/Q abnormalities studied. At time 2, there were significant correlations between BOS and the presence of HPvq (P=0.04, sensitivity 100%, specificity 33%) and SPvq (P=0.04, sensitivity 60%, specificity 83%).

Time point 2 versus time point 1

The presence of HRCT and V/Q abnormalities at time 1 was compared with the development of BOS (FEV_1 less than 80% baseline) at time 2 (Table 6). There were no significant relationships between the presence of any HRCT or V/Q abnormality at time 1 and the presence of BOS at time 2. However, there was a significant correlation between ATvq at time 1 and the grade of BOS at time 2 (P=0.02), with adjusted standardized deviates indicating a greater likelihood of grade 3 BOS at time 2 in patients with ATvq observed at time 1 (Table 6).

Relationship of BOS to MMEF

MMEF less than or equal to 75% at time 1 was found to be significantly related to BOS at time 2 (Table 6, P=0.02, sensitivity 90%, specificity 58%). Figure 1 demonstrates the relationships between FEV_1 per cent baseline and MMEF per cent post-transplant baseline (MMEF per cent baseline) at time 1 and time 2. Of the five patients who developed new BOS (by FEV_1 criteria) at time 2, four had MMEF less than or equal to 75% at time 1. However, there were nine patients at time 1 without BOS in whom the MMEF was less than or equal to 75% of the post-transplant baseline. Of these patients, only four went on to develop BOS at time 2.

TABLE 4
Spirometry and imaging results at time 2 in a study examining noninvasive investigations for the early detection of chronic airways dysfunction following lung transplantation

Subject	FEV_1 % of post-transplant baseline	MMEF % of post-transplant baseline	HRCT MPct	HRCT BDct	HRCT ATct	V/Q ATvq	V/Q HPvq	V/Q SPvq
1	93	60	+	–	–	–	+	–
2	56	31	+	–	+	–	+	–
3	92	76	+	+	+	+	+	+
4	92	68	+	+	+	+	+	–
5	100	34	+	–	–	–	–	–
6	96	52	+	+	+	–	+	–
7	97	75	+	–	+	–	–	–
8	76	35	+	+	+	–	+	–
9	95	81	+	–	–	+	+	–
10	98	96	+	+	+	–	–	–
11	70	22	+	+	+	+	+	+
12	93	64	+	+	+	+	+	+
13	80	37	+	–	–	+	+	–
14	88	70	–	–	–	–	–	–
15	27	8	+	+	+	+	+	+
16	81	26	+	+	+	–	+	–
17	30	18	+	+	+	+	+	+
18	57	16	+	+	+	+	+	+
19	68	34	+	–	+	+	+	+
20	57	26	–	–	–	+	+	–
21	59	22	+	–	+	+	+	+
22	41	9	+	+	+	+	+	–

– Abnormality absent; + Abnormality present; ATct Air trapping on high resolution computed tomography (HRCT); ATvq Air trapping on ventilation/perfusion scan (V/Q); BDct Bronchial dilation on HRCT; FEV_1 Forced expiratory volume in 1 s; HPvq Heterogeneous perfusion on V/Q; MMEF Maximum midexpiratory flow; MPct Mosaic perfusion on HRCT; SPvq Segmental perfusion defect on V/Q

TABLE 5
Relationships of high resolution computed tomography (HRCT), ventilation/perfusion scan (V/Q), and maximum midexpiratory flow (MMEF) with bronchiolitis obliterans syndrome (BOS) at time 2

BOS at time 2 versus:	P	Sensitivity (%)	Specificity (%)
MMEF≤75% post-transplant baseline	0.22	100	25
MPct	0.89	90	8
BDct	0.64	60	50
ATct	0.10	90	42
ATvq	0.07	80	58
HPvq	0.04	100	33
SPvq	0.04	60	83

ATct Air trapping on HRCT; ATvq Air trapping on V/Q; BDct Bronchial dilation on HRCT; HPvq Heterogeneous perfusion on V/Q; MPct Mosaic perfusion on HRCT; SPvq Segmental perfusion defect on V/Q

TABLE 6
Relationships between presence of abnormalities at time 1 with the presence of bronchiolitis obliterans syndrome (BOS) at time 2

BOS at time 2 versus:	P	Sensitivity (%)	Specificity (%)
MMEF≤75% at time 1 post-transplant baseline	0.02	90	58
MPct at time 1	0.64	60	50
BDct at time 1	0.21	60	67
ATct at time 1	0.87	30	67
ATvq at time 1	0.22	40	83
HPvq at time 1	0.57	70	42
SPvq at time 1	0.22	50	75
ATvq at time 1 versus BOS grade at time 2	0.02	–	–

ATct Air trapping on high resolution computed tomography (HRCT); ATvq Air trapping on ventilation/perfusion scan (V/Q); BDct Bronchial dilation on HRCT; HPvq Heterogeneous perfusion on V/Q; MPct Mosaic perfusion on HRCT; SPvq Segmental perfusion defect on V/Q

DISCUSSION

This study was designed to investigate the relationships between HRCT, V/Q and spirometry parameters in stable lung transplant recipients with and without BOS sequentially over a period of several years.

None of the HRCT or V/Q parameters studied were useful (ie, high sensitivity and specificity) for the early detection of BOS, with the exception of ATvq, in which the presence of ATvq at time 1 was significantly related to the severity of BOS at time 2. The only other early indicator for the later development of BOS was a decline in the MMEF to less than or equal to 75% of the post-transplant baseline (P=0.02, sensitivity 90%, specificity 58%).

Chronic airways dysfunction is the major cause of mortality and morbidity in long term survivors of lung transplantation, affecting at least 50% of recipients by three years post-trans-

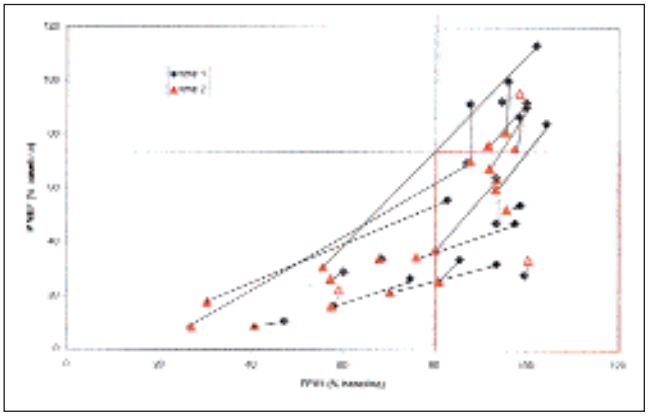

Figure 1) *Relationship between forced expiratory volume in 1 s (FEV_1) (% baseline) and maximum midexpiratory flow (MMEF) (% baseline) in 22 subjects following lung transplantation at two points in time. Each line connects the values observed in a single subject at the two time points 1.5±0.9 years apart (mean ± SD). Black diamonds indicate time point 1, and red triangles indicate time point 2. Of the nine subjects with MMEF less than or equal to 75% baseline but FEV_1 greater than 80% baseline at time 1 (red box), four developed progressive declines in FEV_1 to less than 80% baseline at time 2, while five subjects did not. The dotted lines with open red triangles indicate four subjects in whom the MMEF increased between time 1 and time 2*

plant (2). Although highly specific, the heterogeneous distribution of the chronic rejection process within the transplanted lungs renders invasive diagnosis of OB by transbronchial biopsy unreliable, with sensitivities as low as 17% to 28% (3,4). Hence, the diagnosis of chronic airways dysfunction is generally defined by changes in the FEV_1 (5).

Although a decline in the FEV_1 is a more sensitive marker of chronic airway narrowing than transbronchial biopsy, the loss of function is usually irreversible by the time the diagnosis is made, as evidenced by the failure of increased immunosuppression to reverse the decline in FEV_1 in most cases (1). This suggests that the pathophysiological process is firmly established at the time that BOS is first identified by current spirometric criteria. Therefore, there is a need for a more reliable marker of airways disease following lung transplantation (with high sensitivity and specificity) that will allow for earlier detection of affected patients, in the hopes that changes in immunosuppressive strategies may abort or delay the progression of OB.

Our results differ from most other published reports of the usefulness of HRCT and V/Q scanning in the detection of chronic airways rejection in lung transplant recipients. This may be because of the unique nature of this study in that data from sequential time points were evaluated in all patients. Because we included patients with and without BOS, our study differs from several other studies that included only patients with established OB or BOS in their analysis.

Spirometry for early detection of OB

Because chronic airways rejection is thought to be due to progressive fibrosis and narrowing of the terminal and respiratory bronchioles (19), it has been suggested that the MMEF may be a more sensitive marker of OB than the FEV_1, because it is an earlier indicator of small airways dysfunction (2,5,7,8,19). In a recent study, Bassiri et al (19) studied airway conductance and MMEF in heart-lung and double-lung transplant patients, and found that 46% of the patients with BOS experienced a significant decline (less than 80% of baseline) in the MMEF a median of 367 days before the development of BOS by FEV_1 criteria.

The experience at Stanford (8) would also suggest that MMEF is a more sensitive marker of small airways disease than the FEV_1 in lung transplant recipients. After evaluating the pulmonary function results from all heart-lung and double-lung transplant recipients during a 12-year period, Patterson and colleagues (8) observed that the MMEF fell to less than 70% baseline an average of 112 days before the patients developed International Society for Heart and Lung Transplantation stage 1 BOS. In addition, there was a significantly greater proportional decline from baseline in the MMEF than in the FEV_1 at both time points evaluated.

Keller et al (2) reported similar findings and also demonstrated that a decline in the MMEF of greater than 20% from the post-transplant baseline was associated with a high mortality rate. OB was diagnosed in 16 of 32 lung and heart-lung transplant recipients studied a mean (± SD) of 15.7±14.2 months post-transplant, 15 of whom later had transbronchial biopsy confirmation of the diagnosis a mean of 20±20 months post-transplant. In this group of patients, the mortality was 56% a mean of 8.6±7 months following clinical diagnosis of OB.

In our study population, five of 22 patients had BOS at time 1, with five more patients developing BOS between time 1 and time 2. From a clinical standpoint, the subjects of greatest interest are the ones with low MMEF but normal FEV_1 at time 1 (Figure 1, boxed area). A 25% reduction in the MMEF from the post-transplant baseline was taken to be important, because an MMEF less than or equal to 75% of the post-transplant baseline in the presence of a normal FEV_1 is now labelled as "potential-BOS stage" (5). Although four of five patients who developed new BOS at time 2 had MMEF less than or equal to 75% at time 1 (high sensitivity), there were five other patients with MMEF less than or equal to 75% at time 1 who did not develop BOS at time 2 (low specificity). Hence, the finding of a low MMEF in association with a normal FEV_1 has a poor predictive value. Nevertheless, a falling MMEF in an individual patient may still be an important predictor of developing BOS. Furthermore, it is possible that progressive reductions in FEV_1 would be observed in the low MMEF group with longer follow-up.

Our results are similar to earlier work reported in smokers. In that patient population, declines in the MMEF often precede declines in FEV_1 (7). However, relatively low specificity is also a problem limiting the usefulness of MMEF as an early indicator of small airways disease in that patient population.

HRCT for early detection of OB

There has recently been increasing interest in the use of HRCT for the noninvasive detection of OB. Although there are a number of studies that have demonstrated the usefulness of HRCT in the diagnosis of OB and BOS in patients with established disease, the reported findings have been inconsistent.

In patients with OB related to a variety of causes, including rheumatoid arthritis, bone marrow transplantation, viral infection and single lung transplantation, Padley et al (9) found that the most frequently seen HRCT abnormalities were areas

of decreased attenuation and subsegmental bronchial dilation. Furthermore, there was a significant correlation between the FEV_1 and the number of segments with subsegmental bronchial dilation. Hansell et al (11) also observed areas of decreased attenuation on HRCT scans in all 15 of their patients with OB (related to rheumatoid arthritis, childhood infection, smoking or idiopathic causes) and bronchial wall thickening in 13 of their 15 patients.

Early studies in lung transplant recipients attempted to establish similar relationships between BOS or OB and HRCT. Morrish et al (12) reported the HRCT findings from four patients who had developed biopsy-proven OB following lung transplantation. All four patients had bronchial dilation, and three were found to have decreased peripheral vascular markings. Lentz et al (13) evaluated HRCT scans from 16 heart-lung transplant recipients and found that six of the seven patients with BOS had bronchial dilation in the lower lobes. Similar to Padley et al's study of nontransplant patients with OB (9), there was a significant relationship between the FEV_1 and bronchial dilation (the percentage of dilated lower lobe bronchi). None of these studies reported the sensitivity or specificity of the HRCT abnormalities investigated.

More recently, Leung et al (15) compared the HRCT scans of 11 heart-lung and double-lung transplant recipients who had biopsy-proven OB (mean time from diagnosis of OB 1.3 years) with those from 10 similar patients who did not have OB. They observed bronchial dilation in only 36% of the patients with OB, which was not significantly higher than in those patients without pathological OB (20%). As in the studies by Padley et al (9) and Morrish et al (12), a mosaic pattern of lung attenuation (areas of decreased attenuation) was observed more frequently in patients with OB than controls (64% versus 10%, respectively, $P<0.05$). In addition, they observed that air trapping on expiratory HRCT images was the most sensitive and accurate HRCT indicator of OB, with a sensitivity of 91% and a specificity of 80%.

A more comprehensive evaluation of HRCT changes in 13 lung transplant recipients with and without BOS was reported by Ikonen et al (14). Unlike other investigators, they evaluated HRCT scans for 10 separate abnormalities that were felt to represent chronic changes. These included several abnormalities that were not evaluated in other studies, such as changes in volume, thickening of septal lines and the presence of infiltrates. A score was then given to each HRCT, and this score was found to be significantly related to the decline in FEV_1 and midexpiratory flow at 50% of vital capacity (MEF_{50}). It should be noted, however, that thickening of septal lines and the presence of infiltrates are unlikely to be due to OB. These findings are much more likely due to interstitial lung disease. Furthermore, they observed that the MEF_{50} appeared to be more sensitive than HRCT, in that it often fell before changes were detected on HRCT.

In contrast to the studies reviewed above, we did not find any significant relationships between MPct, BDct or ATct and BOS at a single point in time (Tables 3 and 5). As suggested earlier, the discrepancy between our results and those from previously published work may be due to the differences in study design. Four of the studies outlined above evaluated HRCT abnormalities only in patients having a diagnosis of OB or BOS (9,11-13), whereas our analysis included patients both with and without BOS. Furthermore, the study by Leung et al (15) evaluated HRCT abnormalities in lung transplant recipients with biopsy-proven OB, whereas we evaluated the relationship between HRCT abnormalities and BOS.

One recent study has provided more compelling evidence for a relationship between ATct and BOS. Bankier et al (20) studied 38 heart-lung recipients and eight healthy control patients over seven years with 111 HRCT scans and quantified the amount of air trapping observed on expiratory CT compared with spirometry. They defined a cut-off point of 32% ATct for distinguishing normal patients from those with BOS. There was also a relationship between the degree of BOS and the amount of ATct observed. Like Leung et al (15), they demonstrated a high sensitivity and specifity for ATct (83% and 89%, respectively). Interestingly, of six patients with ATct of greater than 32% and 'normal' FEV_1, five developed BOS at a later date.

V/Q scanning for early detection of OB

The observation that air trapping on ventilation scanning at time 1 was significantly related to the severity of BOS at time 2 is of interest. The limited reported experience in this area involves very small numbers of patients. In a case report by Halvorsen Jr et al (16), a patient with OB following heart-lung transplantation for PPH was found to have nonhomogeneous distribution of Tc-99m aerosol on ventilation scanning, with abnormal distribution of Tc-99m MAA on perfusion lung scanning. In another case report, a patient with OB following single lung transplantation for PPH was found to have a marked V/Q mismatch in the transplanted lung, with 35% of ventilation and 81% of perfusion going to the transplanted lung at the time of diagnosis (21). We observed significant relationships between HPvq and SPvq defects with BOS, but only at time 2, when the number of patients with BOS had doubled. Our results, along with the other cited reports, indicate a possible use for V/Q scanning in suggesting a diagnosis of chronic airways disease following lung transplantation, as well as possibly in predicting which patients may eventually develop BOS.

CONCLUSIONS

In a group of stable, long term lung transplant survivors without concomitant acute rejection or infection, abnormalities on HRCT and V/Q scans or isolated reductions in MMEF did not reliably aid in the early detection of BOS. Although sensitivity was high, HRCT suffered from low specificity. Furthermore, HRCT abnormalities were not predictive for the later development of BOS. Abnormalities on nuclear ventilation imaging were associated with the presence of BOS at time 2 only, but may be predictive of the severity of BOS. Reduced MMEF was significantly related to the development of BOS; however, the finding of a low MMEF in the presence of a normal FEV_1 had a low specificity for predicting the later development of new BOS.

In this small group of lung transplant recipients, MMEF, HRCT and V/Q scanning did not add information that was clinically more useful than FEV_1 in identifying the presence or likely development of chronic airways dysfunction.

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