Thorax Online First, published on February 7, 2006 as 10.1136/thx.2005.051219

Interlobar Collaterals are related to radiological heterogeneity in severe emphysema

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Key words: pulmonary emphysema, collateral ventilation, heterogeneity

Word count: 2317

ABSTRACT

Study Objective: We sought to assess the prevalence of interlobar collateral ventilation in patients with severe emphysema who underwent lung transplantation to identify factors that may help predict patients with significant collateral ventilation.

Methods: Between April 2002 and August 2003, *ex vivo* assessment of the lungs of consecutive 17 patients with smoking related severe emphysema was performed. To assess collateral flow, all lobes of explanted specimens were selectively intubated using a wedged cuffed microlaryngeal intubation tube and then manually ventilated using a bagging circuit. Interlobar collateral ventilation was defined as the ability to easily inflate a non-intubated lobe at physiological pressures. Pre-transplant demographic, physiologic data, radiological results and explant histology were assessed for retrospective relationships with the degree of explanted lung interlobar collateral ventilation.

Results: A total of 23 lungs were evaluated in this study. Fifteen (66%) lung specimens demonstrated significant collateral interlobar airflow. Eight (34%) lung specimens demonstrated no-collateral ventilation between adjacent lobes. There were no significant differences in any demographic, physiologic or pathologic variables between patients with collateral and no-collateral ventilation. However, there was a significant relationship between the presence of interlobar collateral ventilation and radiological scores ($p < 0.05$).

Conclusions: This study demonstrated that interlobar collateral ventilation occurred to a much greater extent in those with radiologically homogeneous emphysema than in those with heterogeneous emphysema. Heterogeneity of emphysema may predict patients with significantly less risk of interlobar collateral ventilation.

INTRODUCTION

Emphysema is a progressive pulmonary disease characterized by abnormal and permanent enlargement of air spaces distal to the terminal bronchioles, accompanied by the destruction of pulmonary parenchyma.[1] Symptoms include breathlessness and exercise limitation due in part to reductions in lung elastic recoil, airway support, and the surface area of the alveolar-capillary bed. Progressive hyperinflation further decreases expiratory flow by compressing the small intraparenchymal airways and ultimately compromises respiratory mechanics, leading to respiratory failure. In the early 1990s, there was renewed interest in the surgical management of severe emphysema, when Lung Volume Reduction Surgery (LVRS) was reintroduced by Cooper and colleagues.[2] The operation was based on the hypothesis that reducing lung size would restore elastic recoil and radial traction on the terminal bronchioles, therefore improving lung function and chest wall mechanics.[3][4][5]

Several controlled trials[6][7][8] demonstrated that LVRS for emphysema improved lung function, exercise capacity[9][10], and quality of life[11]; however, it is also clear that not all patients benefit from LVRS. Moreover, despite careful case selection, and regardless of whether an open sternotomy/thoracotomy or video-assisted approach is utilized, published operative mortality rates vary from 0 to 19%, with postoperative morbidity high.[12][13][14] The National Emphysema Treatment Trial (NETT) indicated that patients who had a very low forced expiratory volume at 1 second (FEV_1, <20% predicted), with either homogeneous emphysema or a very low carbon monoxide diffusing capacity (DLCO) had a high risk of surgical mortality. Recent published data indicates that patients with non-upper-lobe disease have higher operative mortality than upper-lobe predominant patients when undergoing LVRS.[8]

Clearly LVRS can be beneficial, but in recent years, recognizing the cost and morbidity of this major surgery, investigators have vigorously pursued research into innovative alternative methods for achieving Lung Volume Reduction. Many of these new concepts are reaching the stage of clinical trial at this time. One such technique is Bronchoscopic Lung Volume Reduction (BLVR) utilizing bronchial prostheses placed using the fiberoptic bronchoscope to selectively occlude the airways supplying the most affected lobes. This attempts to achieve segmental or lobar atelectasis, simulating the effects of LVRS.[15][16] However, it has been showed that some patients do not achieve significant lobar collapse despite bronchoscopic confirmation of adequate position and function of prostheses. Subsequent bronchoscopy also shows these valve prostheses continue to vent significant amounts of air during expiration. A likely explanation for the unsuccessful lobar collapse is that significant collateral ventilatory connections exist.[17][18]

There is a paucity literature regarding the incidence, extent or etiology of interlobar collaterals in severe emphysema patients. The specific purpose of this study was: (i) to assess the prevalence of interlobar collateral channels in patients with severe emphysema who underwent lung transplantation and (ii) to identify factors that may help predict patients with significant collateral ventilation.

METHODS

Patients and Data Collection

This study was approved by the Medical Ethical Committee of the Alfred Hospital. Seventeen consecutive patients with smoking related severe emphysema undergoing lung transplantation at the Alfred Hospital between April 2002 and August 2003 were included in this study. Patients with emphysema associated with α_1-antitrypsin deficiency were excluded from this study. Preoperative patient demographics and physiologic data are outlined in Table 1. Ten patients underwent single and 7 patients underwent bilateral sequential lung transplantation. Patient ages ranged from 49 to 64 years [mean, 57 (5.4) yr], and there were 4 women and 13 men. Ten patients used continuous oxygen, and the remaining 7 patients used oxygen with activity and sleep. All patients were receiving an inhaled β-agonist and inhaled steroid. Ten patients were also receiving oral corticosteroids.

Physiological data was collected from lung function and radiological studies performed at the time of listing for lung transplantation. Lungs were stored at 4^0C if not immediately assessed and all studies were performed within 24 hours of the transplant procedure.

Table 1. Patient Demographics and Physiologic Data
(17 patients)

Demographics	
Age (yrs)	57 (5.4)
Gender	Female; 4 Male; 13
Pack-years	39 (25-70)
Oral Steroids	10
Inhaled Steroids	17
Oxygen dependent	10
Lung Function [L, % Predicted]	
FEV_1	0.59 (0.20) [19 (6.3)]
FVC	1.96 (0.63) [55 (15)]
RV	5.53 (1.24) [250 (52)]
TLC	7.90 (1.58) [136 (13)]
DLCO	7.50 (2.40) [26 (9.0)]
Arterial Blood Gases (on room air)	
PaO_2 (mmHg)	69 (13)
$PaCO_2$ (mmHg)	51 (10)
6-min Walk Distance (m)	319 (266-373)

Data are presented as mean (SD) or medians (interquartile range)

Pulmonary Function Testing

Pulmonary function testing was performed for each patient before transplantation using body plethysmography (Medgraphics Corporation; St. Paul, MN) with Breeze PF software version 3.8B.204 system (Medical Graphics; St. Paul, MN) according to The American Thoracic Society standard. Arterial blood gas analysis was performed with the patient sitting, at rest, breathing room air. The 6-minute walking distance was performed with experienced supervision according to published methods without oxygen supplementation.[16]

Radiologic Evaluation and Scoring

CT imaging and scoring.

The distribution and severity of emphysema were determined from high-resolution computed tomographic (CT) scans of the chest obtained during full inspiration. Selection thickness was 1-mm, with a 10-mm intersection interval.

The chest CT was reviewed and scored by a radiologist, blinded to clinical or physiological information. The system scored the extent of emphysema on the CT scans and was adapted from prior work by several authors.[19][20][21] All sections above the level of the diaphragm were assessed individually, and the right and left lungs were graded separately according to the percentage area that demonstrates changes (low attenuation, lung destruction, and vascular disruption) suggestive of emphysema. A score of 1 represents destruction of 1%-25% of the lung by emphysema; a score of 2, destruction of 26%-50% of the lung; a score of 3, destruction of 51%-75% of the lung;

and a score of 4, destruction of 76%-100% of the lung. Each lung was divided into three apical-to-basal zones on a number of slices. Each zone was scored in the following manner: A maximum possible score for the zone was obtained by multiplying the number of CT slices within a zone by 4, the maximum possible score per CT slice. The actual cumulative zone score was determined by adding all of the actual scores of each slice within that zone, and then divided by the maximum possible score to get a percentage within that zone. Heterogeneous emphysema was defined as a difference in scores of at least two among the three zones in one lung; otherwise, the distribution of emphysema was classified as homogeneous. In addition, the radiologist classified the distribution of emphysema as predominantly affecting the upper lobes, predominantly affecting the lower lobes, diffuse, or predominantly affecting the superior segments of the lower lobes; the latter three categories were grouped together as purposes of our analysis.

V/Q imaging and scoring

Standard six views planar ^{99m}Tc-MMA perfusion scintigrapy was performed on a 2-headed large field of view gamma camera (General Electric Medical Systems, Milwaukee, USA) with a low energy, window of 70keV. Each patient received 111 MBq (3 mCi) of technetium-labeled macro-aggregated albumin (Brigham and Women's Hospital, Boston, Mass). The radiologist was blinded to any clinical, physiological, and CT data. The scoring system used for visual assessment was described by Ingenito et al[22] and is as follows: An upper/lower perfusion ratio (ULPR) index was utilized for identifying patients with heterogeneous upper lobe predominant disease. This index is calculated as the ratio of upper lobe perfusion to lower lobe perfusion (U/L). Patients were classified as having homogeneously distributed disease if their ULPR was between 0.75 and 1.25. Patients with ULPR indices outside this range were classified as having heterogeneous disease.

Explanted Lung Studies

The procedures for assessing the presence of collateral ventilation have been described previously.[23] Post explantation, after passive deflation, lungs were macroscopically examined to define lobar anatomy and graded interlobar fissuring. The extent of the interlobar fissuring was assessed in each fissure: absent = no fissure; minimal = fissure less than 25% of potential area from pleural interface to hilum; moderate = 25%-75%; and complete = more than 75%. All lobes of explanted specimens were selectively intubated using a wedged cuffed microlaryngeal intubation tube (size 4; Mallinckrodt Medical, Athlone, Ireland) and then manually ventilated using a bagging circuit at physiological inflation pressures. Interlobar collateral ventilation was defined as the ability to easily inflate a non-selected (i.e. non-intubated) lobe at physiological pressures.

Histopathology

The explanted tissue was sectioned in approximately the same regions in slices 0.2- to 0.4-cm thickness and embedded in paraffin. Slides were stained with hematoxylin-eosin by standard methods. Histologic specimens from all lobes of explanted lung were reviewed by an experienced pathologist, blinded to clinical information.

Statistical Analysis

All analysis was performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). Comparisons of proportions were made using chi-square tests for equal proportion or Fishers exact tests where numbers were small. Continuous variables were compared using student t-tests and validated with Wilcoxon rank sum tests. While no significant autocorrelation could be found between the six repeated subjects, all significant results were further validated by the removal of all repeat measures. A two sided p-value of 0.05 was considered to be statistically significant. Continuous data are expressed as mean and standard deviation (SD) where normally distributed, and as medians (InterQuartile range) otherwise.

RESULTS

Explanted Lung Studies

A total of 23 lung specimens were evaluated, 12 left lung and 11 right lung in this study. The data concerning the side studied and the extent of interlobar fissuring is shown in Table 2A. Collateral interlobar airflow was seen in 15 of 23 specimens, and its prevalence was 66%. Three of 6 bilateral lung transplant patients showed collateral ventilation in one lung but none in the other. The lung specimens were classified into two groups consisting of 15 specimens with collateral ventilation and 8 specimens with no-collateral ventilation. There were no significant differences between collateral ventilation and the extent of interlobar fissures ($p = 0.33$) (Table 2B). Although the lingual is not usually described as a separate lobe, on one occasion the left lower lobe had communication with the left upper lobe (but not the lingula) and on another occasion the left lower lobe communicated with the lingual (but not the remaining left upper lobe).

Table 2A. Incidence of Collateral Ventilation
(23 Lungs)

Collateral Ventilation	n
All lobes	5 (22%)
Lower - Upper	3 (13%)
Middle (Lingula) - Upper	2 (9%)
Lower - Middle (Lingula)	2 (9%)
Lower - Upper & Middle - Upper	3 (13%)
None	8 (34%)
Total	23

Table 2B. Collateral Ventilation and Extent of Interlobar Fissuring

Extent of Interlobar Fissuring	Collateral Ventilation	No-Collateral Ventilation	Total
Absent	0	0	0
Minimal	1	2	3
Moderate	9	4	13
Complete	5	2	7
Total	15	8	23

Comparison of Collateral Ventilation vs No-Collateral Ventilation Lungs

Demographic data and pulmonary function results for the collateral group and the no-collateral group were summarized in Table 3. There were no significant differences in all variables between the two groups whether considered as individual or paired lungs.

Table 3. Comparison of Collateral *vs* No-Collateral Ventilation Lungs

	Collateral (n = 15) Ventilation	No-Collateral (n = 8) Ventilation	*p* value
Age	56.3 (5.07)	58.0 (6.14)	0.49
Male : Female	11 : 4	6 : 2	0.95
Pack Years	30 (24-70)	42 (27-75)	0.46
FEV_1, L	0.65 (0.22)	0.58 (0.16)	0.42
FEV_1 %predicted	20.8 (6.30)	20.0 (6.80)	0.78
FVC, L	2.20 (0.54)	2.04 (0.81)	0.59
FVC %predicted	57.0 (12)	56.0 (21)	0.91
FEV_1/FVC	0.30 (0.06)	0.30 (0.07)	0.91
RV, L	5.29 (0.83)	5.37 (1.87)	0.88
RV %predicted	258 (33)	264 (79)	0.79
TLC, L	8.04 (1.36)	8.09 (2.04)	0.94
TLC %predicted	132 (12)	134 (16)	0.73
DLCO	7.80 (2.30)	8.80 (2.60)	0.36
DLCO %predicted	28.0 (8)	28.5 (10)	0.35
Pa O_2, mmHg	66 (12)	70 (15)	0.41
Pa CO_2, mmHg	53 (8)	52 (13)	0.89
6-Minutes Walk, m	314 (280-360)	339 (247-388)	0.75

Data are presented as mean (SD) or medians (interquartile range)

The relationship between Collateral Ventilation and Retrospective Radiologic Scores

Radiologic scores were shown in Table 4. CT scores of emphysema heterogeneity; 10 (50%) of 20 available CT scans fulfilled the criteria of homogeneous emphysema (9 specimens with collateral ventilation and one specimen with no collateral ventilation) and 10 specimens fulfilled the criteria of heterogeneous emphysema (4 specimens with collateral ventilation and 6 specimens no collateral ventilation). There was significant relationship between collateral ventilation and heterogeneity of emphysema for chest CT scoring ($p = 0.05$), with the result becoming slightly more significant when repeat data was removed ($p = 0.02$). There was no significant relationship between the CT extent of fissuring and the presence of collateral ventilation (data not shown).

Scintigraphic scores of perfusion heterogeneity; 9 (41%) of 22 available perfusion scans fulfilled the criteria of homogeneous emphysema (8 specimens with collateral ventilation and one specimen with no collateral ventilation). On the other hand, 13 specimens fulfilled the criteria of heterogeneous emphysema (6 specimens with collateral ventilation and 7 specimens with no collateral ventilation). There was a significant relationship between collateral ventilation and heterogeneity of disease for perfusion scintigraphic scoring that remained apparent when repeat measures were removed ($p < 0.05$).

Matching/mismatching of chest CT score and perfusion scintigraphic score for individual lungs in the two groups are shown in Table 5. In collateral ventilation, 4 (20%) specimens

had a matched homogeneous picture, where both chest CT scores and perfusion scintigraphic scores showed the criteria of homogeneous emphysema. Furthermore, 5 (25%) specimens had a matched heterogeneous picture and no-collateral ventilation. There was a significant relationship between collateral ventilation and radiological scores ($p = 0.04$) that was not altered when repeat measures were removed.

Table 4. Heterogeneity of Emphysema for Chest CT and V/Q Scintigraphic Scores

	Collateral Ventilation	No-Collateral Ventilation	*p* value
CT Scores of Heterogeneity			0.05
homogeneous	9	1	
heterogeneous	4	6	
Scintigraphic Scores of Heterogeneity			0.04
homogeneous	8	1	
heterogeneous	6	7	

Table 5. Correlation between Collateral Ventilation and Radiological Findings

CT Scores - Scintigaphic Scores	Collateral Ventilation	No-Collateral Ventilation
*Matched Homogeneous	4	1
Mismatched	7	1
Matched Heterogeneous	2	5

*Matched = concomitant CT and Perfusion scores

Histopathologic results

Lungs from all lobes had some degree of emphysema characterized by disruption of the alveolar walls with formation of extended open airspaces. Emphysema was represented as moderate to severe in all lobes. Nine (39%) patients had centrilobular, 10 (43%) patients had panacinar, and 4 patients had mixed (centrilobular and panacinar) emphysema. This classification did not relate to the presence of interlobar collaterals (data not shown).

DISCUSSION

The main findings of this study were: 1) Functionally sizable collateral channels are frequent between lobes in emphysema. Given that there are bronchoscopic attempts to exclude lobes to emulate LVRS, the likelihood is that 66% of lobar occlusions will not result in significant volume loss due to the presence of these interlobar collaterals. 2) The degree of heterogeneity on CT and V/Q scintigraphy does, in part, predict the likelihood of collaterals (i.e. those judge to have homogeneous disease are highly likely to have interlobar collaterals).

The presence of collateral ventilation was first confirmed by Van Allen and colleagues in 1930. Collateral ventilation is present in the normal lung, but its importance in the distribution of ventilation is negligible because the resistance to airflow is higher in

collateral channels than in the airway.[24] Observations in postmortem emphysematous human lungs demonstrated, however, that the resistance to collateral airflow in the lungs of patients with emphysema is low in comparison with that in normal lungs.[17] Three levels of collateral ventilation have previously been described in human lungs. The 1-2 μm pores of Kohn[25], the 30μm channels of Lambert[26], and the 80-150 μm interbronchiolar communications in humans were described by Martin.[27] Morrell et al discovered that segmental collateral ventilation occurred to a much greater extent in the emphysematous lung than in the normal lung.[28]

Although surprisingly not described in the more recent reviews, the older medical literature provides some support for the concept of poorly characterized interlobar communications. Hogg et al first considered the possibility of collateral ventilation in patients with emphysema, demonstrating intralobar collateral ventilation between segments and interlobar collateral ventilation across the major fissure in patients with emphysema.[17] Rosenberg and Lyons demonstrated significant interlobar collateral ventilation occurring at physiological pressures in five excised lungs with emphysema and pneumonia. Furthermore, they carried out radioactive ^{133}Xenon studies on some of the lung preparations after the collateral flow measurements were made.[29] Recently, other investigators have described that ventilation scintigraphy using ^{133}Xenon performed on days 3 and 15 after BLVR prostheses placement demonstrated reduced and delayed wash-in of ^{133}Xenon into the ostensibly occluded upper lobes and accelerated wash-out of ^{133}Xenon from the non-occluded lower lobes.[23] The faster wash-out of the lower lobes and persistent upper lobe ventilation are most likely the result of diffusion of ^{133}Xenon into the upper lobes through interlobar collaterals.

We sought to identify factors that may help predict patients with significant interlobar collateral ventilation. Van Allen et al found that gas diffusion occurred easily within lobes but only crossed the fissure when the lobes was overdistended.[24] Our data demonstrated that air might flow through interlobar collateral channels betweens lobes at physiological pressures and it is notable that all patients were hyperinflated. However, there was no statistical relationship between collateral ventilation and the extent of interlobar fissure or the exact degree of hyperinflation. In fact, a comparison between the collateral group and the no-collateral group noted there was no significant difference in any demographic on pulmonary functional variables. In particularly, our results did not indicate that collateral ventilation was increased with age as has been previously reported.[30]

Interestingly, we find that there were significant relationship between collateral ventilation and radiological scores ($p = 0.04$). This finding suggests that interlobar collateral ventilation occurred to a much greater extent in the homogeneous emphysema

than in the heterogeneous emphysema. We recognize the limitations of our study, namely the analysis of only the severe end of the spectrum patients and the use of 1 or 2 lungs from included patients (although no differences were noted when repeat measures were removed, the sample size is inherently small). The other major issue is the lack of a "gold standard visual scoring system" regarding emphysema heterogeneity. Nuclear V/Q scintigraphy has proved useful in demonstrating the considerable heterogeneity of the pattern of emphysema.[31] However, when applying a semiquantitative scoring system of visual assessment of perfusion scintigrams, correlation between scores of perfusion heterogeneity and functional outcome has been weak.[32] The mismatch relationship between heterogeneity scores from chest CT and V/Q scintigraphy has two main implications: First, it confirms that the two techniques measure different properties of the lungs, namely, structure and function, respectively, and therefore provide complementary information. Second, the low prevalence of a homogeneous distribution in V/Q scintigraphy demonstrates that the technique is relatively sensitive for subtle differences in regional lung function (as reflected by perfusion) even in patients in whom visual inspection of the chest CT suggests an even distribution of structural alterations by emphysema among all lung areas.

Much of the controversy surrounding LVRS involves the variability of response among patients, limitations in the magnitude of response, costs and concerns about the duration of improvement. Air leak remains the major morbidity following LVRS. Knowledge of the precise incidence, extent and etiology of interlobar collaterals may be important to predicting the likely success of LVRS and innovative alternative strategies (such as bronchoscopic valves, prostheses, or glues) for severe emphysema.

Interlobar collateral ventilation in emphysema may explain clinically observed phenomena such as persistent air-leaks post-lobectomy or post-segmentectomy, the failure of lobes to collapse when selectively intubated in intensive care or during anesthesia and the development of giant bullae in some patients with emphysema.[33] Furthermore, there may also be relevance to the spread of infectious pathogens and malignant cells between lobes. More research is warranted to find other techniques to allow prediction of those patients without interlobar collateral ventilation who might be more likely to benefit from bronchoscopic lung volume reduction techniques and to link interlobar collateral ventilation with local/nodal lung cancer metastatic spread patterns.

In conclusion, it is apparent from the present study that interlobar collateral ventilation is an underrecognised significant phenomenon (66% in the present study) in severe emphysema that may have important pathophysiology correlates for a range of clinical circumstances. Although a comparison between the collateral group and the no-collateral group revealed no significant differences in any demographic, pulmonary functional, or

histopathological variables, interlobar collateral ventilation occurred to a much greater extent in those with radiologically homogeneous emphysema than in those with heterogeneous emphysema. Therefore, heterogeneity of emphysema may predict patients with significant or less risk of interlobar collateral ventilation. And, future studies need to address the particular relevance of interlobar collaterals to the success of LVRS techniques.

Acknowledgments

We wish to thank Anna Reed for data collection and Michael J Bailey for statistical advice.

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