EMPHYSEMA

Relation of interlobar collaterals to radiological heterogeneity in severe emphysema

T Higuchi, A Reed, T Oto, L Holsworth, S Ellis, M J Bailey, T J Williams, G I Snell

Background: A study was undertaken to assess the prevalence of interlobar collateral ventilation in patients with severe emphysema to identify factors that may help to predict patients with significant collateral ventilation.

Methods: Between April 2002 and August 2003, ex vivo assessment of the lungs 17 consecutive 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 characteristics, physiological data, radiological results, and explant histology were assessed for retrospective relationships with the degree of interlobar collateral ventilation in the explanted lung.

Results: A total of 23 lungs were evaluated, 15 of which (66%) had significant collateral interlobar airflow. There were no significant differences in any demographic, physiological, or pathological variables between patients with collateral ventilation and those with no collateral ventilation. However, there was a significant relationship between the presence of interlobar collateral ventilation and radiological scores (p<0.05).

Conclusions: Interlobar collateral ventilation occurs to a much greater extent in patients with radiologically homogeneous emphysema than in those with heterogeneous emphysema. Heterogeneity of emphysema may predict patients with a significantly reduced risk of interlobar collateral ventilation.

Methods

Patients and data collection

This study was approved by the medical ethical committee of the Alfred Hospital. Seventeen consecutive patients (13 men) with smoking related severe emphysema undergoing lung transplantation at the Alfred Hospital between April 2002 and August 2003 were included in the study. Patients with major surgery and 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) which uses bronchial prostheses placed using a 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. However, it has been shown that some patients do not achieve significant lobar collapse despite bronchoscopic confirmation of adequate position and function of the prostheses. Subsequent bronchoscopic examination also shows that 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. There is a paucity of literature regarding the incidence, extent, or aetiology of interlobar collaterals in patients with severe emphysema. The purpose of this study was to assess the prevalence of interlobar collateral channels in patients with severe emphysema who underwent lung transplantation and (to identify factors that may help predict patients with significant collateral ventilation.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LVRS, lung volume reduction surgery; TLCO, carbon monoxide transfer factor; ULPR, upper/lower perfusion ratio
emphysema associated with α1-antitrypsin deficiency were excluded. Preoperative patient demographic and physiological data are shown in table 1. Ten patients underwent single lung transplantation and seven underwent bilateral sequential lung transplantation. The mean (SD) age of the patients was 57 (5.4) years (range 49–64). Ten patients used continuous oxygen and the remaining seven used oxygen with activity and sleep. All patients were receiving an inhaled β agonist and inhaled steroid; 10 patients were also receiving oral corticosteroids.

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

Pulmonary function testing
Pulmonary function testing was performed for each patient before transplantation using body plethysmography (Medgraphics Corporation, St Paul, MN, USA) with Breeze PF software version 3.8B.204 system (Medical Graphics St. Paul, MN, USA) with Breeze before transplantation using body plethysmography

Table 1

| Patient demographic and physiological data (17 patients) |
|-----------------|-----------------|-----------------|
| Age (years)     | 57 (5.4)        |                 |
| Sex (F:M)       | 4:13            |                 |
| Pack years      | 39 (25–70)      |                 |
| Oral steroids   | 10              |                 |
| Inhaled steroids| 17              |                 |
| Oxygen dependent| 10              |                 |
| Lung function (1, % predicted) | 0.59 (0.20), 19 (6.3) |         |
| FVC             | 1.96 (0.63), 55 (13) |           |
| RV              | 5.53 (1.24), 250 (52) |         |
| TLC             | 7.90 (1.58), 136 (13) |        |
| TCO2            | 7.50 (2.40), 26 (9.0) |        |
| Arterial blood gases (on room air) | 9.2 (1.7) | 6.8 (1.3) |
| PaCO2 (kPa)     | 6.8 (1.3)       |                 |
| 6 min walk distance (m) | 319 (266–373) |                 |

Data are presented as mean (SD) or median (interquartile range).

V/Q imaging and scoring
Standard six view planar 99mTc-MMA perfusion scintigraphy was performed on a two-headed large field of view gamma camera (General Electric Medical Systems, Milwaukee, USA) with a low energy window of 70 keV. Each patient received 111 MBq (3 mCi) of technetium labelled macro-aggregated albumin (Brigham and Women’s Hospital, Boston, MA, USA). The radiologist was blinded to any clinical, physiological, and CT data. The scoring system used for visual assessment was described by Ingenito et al and is as follows: an upper/lower perfusion ratio (ULPR) index was used for identifying patients with heterogeneous upper lobe predominant disease. This index is calculated as the ratio of upper lobe to lower lobe perfusion (UL/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. 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 lobe: 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 (that is, non-intubated) lobe at physiological pressures.

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

Statistical analysis
All analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC, USA). Comparisons of proportions were made using χ2 tests for equal proportion or Fisher’s exact tests where numbers were small. Continuous variables were compared using Student’s 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) when 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). The data concerning the side studied and the extent of interlobar fissuring are shown in table 2. Collateral interlobar airflow was seen in 15 of 23 specimens (prevalence of 66%). Three of the six patients who underwent bilateral lung transplantation had 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 eight with no collateral ventilation. There were no significant differences between collateral ventilation and the extent of interlobar fissures (p = 0.33, table 3). Although the lingula 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 lingula (but not the remaining left upper lobe).

Comparison of collateral ventilation versus no collateral ventilation lungs
Demographic data and pulmonary function results for the collateral group and the no collateral group are summarised in table 4. There were no significant differences in any of the variables between the two groups whether considered as individual or paired lungs.

Relationship between collateral ventilation and retrospective radiological scores
Radiological scores are shown in table 5. CT scores of emphysema heterogeneity: 10 of the 20 available CT scans fulfilled the criteria for homogeneous emphysema (nine with collateral ventilation and one with no collateral ventilation) and 10 fulfilled the criteria for heterogeneous emphysema (four with collateral ventilation and six with no collateral ventilation). There was a 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 were 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: nine of 22 available perfusion scans (41%) fulfilled the criteria for homogeneous emphysema (eight with collateral ventilation and one with no collateral ventilation) and 13 fulfilled the criteria for heterogeneous emphysema (six with collateral ventilation and seven 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 scores and perfusion scintigraphic scores for individual lungs in the two groups are shown in table 6. Of the specimens with collateral ventilation, four (20%) had a matched homogeneous picture with both chest CT scores and perfusion scintigraphic scores showing the criteria for homogeneous emphysema. Furthermore, five specimens (25%) 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.

Histopathological results
Lungs from all lobes had some degree of emphysema characterised by disruption of the alveolar walls with formation of extended open air spaces. Emphysema was represented as moderate to severe in all lobes. Nine patients (39%) had centrilobular emphysema, 10 (43%) had panacinar emphysema, and four 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 sizeable 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; and (2) the degree of heterogeneity on CT and V/Q scintigraphy does, in part, predict the likelihood of collaterals—that is, those judged 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. Observations in necropsy emphysematous human lungs, however, showed that the resistance to collateral airflow in the lungs of patients with emphysema is low in comparison with that in normal lungs. Three levels of collateral ventilation have previously been described in human lungs: 1–2 μm pores of Kohn, 30 μm channels described by Lambert, and 80–150 μm interbronchiolar communications in humans described by Martin. Morrell et al discovered that segmental collateral ventilation occurred to a much greater extent in the emphysematous lung than in the normal lung.

Although surprisingly not described in the more recent reviews, the older medical literature provides some support for the concept of poorly characterised 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. 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.\textsuperscript{24} Other investigators have recently reported that ventilation scintigraphy using $^{133}$Xenon performed on days 3 and 15 after placement of BLVR prostheses showed 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.\textsuperscript{30} 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 to 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 were overdistended.\textsuperscript{24} Our findings show that air might flow through interlobar collateral channels between 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 showed no significant differences in any demographic characteristic on pulmonary functional variables. In particular, our results did not indicate that collateral ventilation increased with age, as has previously been reported.\textsuperscript{30} Interestingly, we found a significant relationship between collateral ventilation and radiological scores ($p = 0.04$). This finding suggests that interlobar collateral ventilation occurs to a much greater extent in homogeneous emphysema than in heterogeneous emphysema.

We recognise that our study has some limitations. Firstly, we analysed patients only at the severe end of the spectrum and used one or two 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.\textsuperscript{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.\textsuperscript{32} The mismatch relationship between heterogeneity scores from chest CT scans and V/Q scintigraphy has two main implications: (1) it confirms that the two techniques measure different properties of the lungs—namely, structure and function, respectively—and therefore provide complementary information; and (2) the low prevalence of a homogeneous distribution in V/Q scintigraphy shows 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 scan suggests an even distribution of structural alterations by emphysema among all lung areas.

Much of the controversy surrounding LVRS involves the variability of the response by patients, limitations in the magnitude of the response, costs, and concerns about the duration of improvement. Air leak remains the major morbidity following LVRS. Knowledge of the precise incidence, extent, and aetiology of interlobar collaterals may be important in predicting the likely success of LVRS and

![Table 4](image)

<table>
<thead>
<tr>
<th></th>
<th>Collateral ventilation (n = 15)</th>
<th>No collateral ventilation (n = 8)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.3 (5.07)</td>
<td>58.0 (6.14)</td>
<td>0.49</td>
</tr>
<tr>
<td>M:F</td>
<td>11:4</td>
<td>6:2</td>
<td>0.95</td>
</tr>
<tr>
<td>Pack years</td>
<td>30 (24–70)</td>
<td>42 (27–75)</td>
<td>0.46</td>
</tr>
<tr>
<td>FEV(_1) (l)</td>
<td>0.69 (0.22)</td>
<td>0.58 (0.14)</td>
<td>0.42</td>
</tr>
<tr>
<td>FEV(_1) (% predicted)</td>
<td>20.8 (6.30)</td>
<td>20.0 (6.80)</td>
<td>0.78</td>
</tr>
<tr>
<td>FVC (l)</td>
<td>2.20 (0.54)</td>
<td>2.04 (0.81)</td>
<td>0.59</td>
</tr>
<tr>
<td>FVC (% predicted)</td>
<td>57.0 (12)</td>
<td>56.0 (21)</td>
<td>0.91</td>
</tr>
<tr>
<td>FEV(_1)/FVC</td>
<td>0.30 (0.06)</td>
<td>0.30 (0.07)</td>
<td>0.91</td>
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<tr>
<td>RV (l)</td>
<td>5.29 (0.83)</td>
<td>5.37 (1.87)</td>
<td>0.88</td>
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<tr>
<td>RV (% predicted)</td>
<td>258 (33)</td>
<td>264 (79)</td>
<td>0.79</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>8.04 (1.36)</td>
<td>8.09 (2.04)</td>
<td>0.94</td>
</tr>
<tr>
<td>TLC (% predicted)</td>
<td>132 (12)</td>
<td>134 (16)</td>
<td>0.73</td>
</tr>
<tr>
<td>TlCO (ml/min/mmHg)</td>
<td>7.8 (2.3)</td>
<td>8.8 (2.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>TlCO (% predicted)</td>
<td>28.0 (8)</td>
<td>28.5 (10)</td>
<td>0.35</td>
</tr>
<tr>
<td>PaO(_2) (kPa)</td>
<td>8.8 (1.6)</td>
<td>9.3 (2.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>PaCO(_2) (kPa)</td>
<td>7.1 (1.1)</td>
<td>6.9 (1.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>6 min walk (m)</td>
<td>314 (280–360)</td>
<td>339 (247–388)</td>
<td>0.75</td>
</tr>
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</table>

Data are presented as mean (SD) or median (interquartile range).

![Table 5](image)

<table>
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<th>Collateral ventilation</th>
<th>No collateral ventilation</th>
<th>p value</th>
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<tbody>
<tr>
<td>CT scores of heterogeneity</td>
<td>9</td>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>8</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Scintigraphic scores of heterogeneity</td>
<td>6</td>
<td>7</td>
<td></td>
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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 following lobectomy or segmentectomy, the failure of lobes to collapse when selectively intubated in intensive care or during anaesthesia, and the development of giant bullae in some patients with emphysema.\(^1\) They may also be relevant to the spread of infectious pathogens and malignant cells between lobes. More research is needed to find other techniques which will predict 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 pathophysiological correlates for a range of clinical circumstances. Although a comparison between the collateral and no collateral groups revealed no significant differences in any demographic, pulmonary function, or histopathological variables, 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 therefore predict patients with a significant or reduced risk of interlobar collateral ventilation. Future studies need to address the particular relevance of interlobar collaterals in the success of LVRS techniques.

ACKNOWLEDGEMENTS

The authors thank Anne Reed for data collection and Michael J Bailey for statistical advice.

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Funding: none.

Competing interests: none declared.

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Thorax 2006 61: 409-413 originally published online February 7, 2006
doi: 10.1136/thx.2005.051219

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