Atelectasis and survival after bronchoscopic lung volume reduction for COPD

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Abstract

Background: Bronchoscopic therapies to reduce lung volumes in COPD are intended to avoid the risks associated with lung volume reduction surgery, or to be used in patient groups in whom LVRS is not appropriate. **Aims**: Bronchoscopic lung volume reduction, using endobronchial valves, to target unilateral lobar occlusion can improve lung function and exercise capacity in patients with emphysema. Benefit is most pronounced in, though not confined to, patients where lobar atelectasis occurred. Few data exist on their long term outcome. **Methods**: 19 patients (16 male) FEV_1 28.4(11.9) underwent BLVR between July 2002 and February 2004. Radiological atelectasis was observed in 5 patients. Survival data to February 2010 was available for all patients. **Results:** None of the patients in whom atelectasis occurred died during follow up whereas 8 out of 14 in the non-atelectasis group died (Chi^2 p=0.026). There was no significant difference between the groups at baseline in lung function, quality of life, exacerbation rate, exercise capacity (shuttle walk test or cycle ergometry) or CT appearances, although BMI was significantly higher in the atelectasis group 21.6(2.9) vs 28.4(2.9)$kg.m^{-2}$ ($p<0.001$). **Conclusions** These data suggest that atelectasis following BLVR is associated with a survival benefit which is not explained by baseline differences.

Keywords Emphysema, mortality, interventional bronchoscopy

INTRODUCTION

Despite optimal pharmacological therapy and pulmonary rehabilitation, patients with chronic obstructive pulmonary disease remain significantly disabled. Lung volume reduction surgery (LVRS) has been clearly shown to improve outcomes in selected patient groups [1-3]. The surgical intervention is however, associated with significant morbidity and an early mortality rate of about 5% [1, 2]. There is considerable interest in developing novel treatment approaches that can reduce lung volumes and gas trapping, either more safely than LVRS, or else in patients for whom LVRS is not an option [4]. These include: the placement of endobronchial valves to prevent airflow to worst affected areas; the PneumRx^{TM} coil to compress emphysematous lung; the creation of airway bypasses to allow trapped gas to escape and the bronchoscopic instillation of biologic agents to achieve volume reduction [4-17].

As this is a rapidly developing area, few data exist regarding the long term outcome of these approaches. There is an urgent need for therapies that might improve prognosis in COPD. Although pharmacological therapies are effective in relieving breathlessness and improving exercise capacity and quality of life, only smoking cessation and, in the most hypoxic individuals, oxygen therapy, have been shown to improve survival. In 2005 the authors published a case series describing the effect of bronchoscopic lung volume reduction (BLVR), using the Emphasys^{TM} valves in patients with severe emphysema. The procedure was associated with improvements in exercise capacity that were most pronounced in, but not confined to, individuals with radiological atelectasis[14]. It is not known whether success of the procedure is associated with long term benefit. This knowledge would inform the ongoing debate

as to whether lobar atelectasis should be the target of valve therapy. This approach involves all segments of a target lobe being occluded and patients selected according to the presence of intact interlobar fissures, a marker of the absence of interlobar collateral ventilation. However the occurrence of atelectasis may increase the risk of pneumothorax as the lung tissue remodels[9] and since some benefit occurs in the absence of atelectasis some investigators prefer a less extensive strategy without lobar occlusion[16]. Long term survival of patients from the authors' original study was reviewed and related to treatment response and baseline characteristics.

METHODS

Between July 2002 and February 2004 19 patients (16 male), FEV_1 28.4(11.9) %predicted underwent BLVR at The Royal Brompton Hospital. Vital status was established for all the participants up to February 2010 (i.e. 6 years after the last procedure was completed) and survival data censored at 6 years. Clinical records were also reviewed for evidence of late complications that might have been due to the valves such as pneumothorax or distal pneumonia. Where patients had died a copy of their death certificate was obtained to establish the cause of death.

A full description of the original trial cohort, methods and four week outcomes has been published previously [14]. To recap briefly, patients were eligible to participate if they had COPD consistent with the GOLD guidelines [18], significant dyspnoea despite optimum medical therapy including pulmonary rehabilitation and a heterogeneous pattern of disease with a target area identified by CT scanning and

ventilation perfusion scintigraphy [15]. The Royal Brompton Hospital's Research Ethics Committee approved the study and patients gave their informed consent.

Endobronchial occlusion was performed using one-way valves (Emphasys Medical, Inc, Redwood City, Ca), placed to occlude segmental bronchi leading to the most affected area of lung. All procedures were unilateral. Initially, valves were inserted on a single occasion under general anaesthesia [15, 19]. Subsequently some procedures were carried out with sedation only and some of these were staged, with valves being inserted on two separate occasions one to two weeks apart. A radiologist blinded to clinical outcome assessed CT evidence of atelectasis, defined as changes in the position of interlobar fissures adjacent to the targeted area in CT scans performed one month post procedure.

Spirometry, gas transfer and lung volumes assessed by body plethysmography were measured using a CompactLab System (Jaeger, Hoechberg, Germany). PaO_2 and $PaCO_2$ were measured in arterialized earlobe capillary samples. Quality of life was assessed using the St George's respiratory questionnaire (SGRQ) and the Short form-36 (SF-36).

Patients performed endurance cycle ergometry, at 80% of the maximum workload achieved on a previous incremental test, before and after BLVR. Improvers were defined as those who had $\geq$60 seconds and 30% increase in endurance time.

Pre-treatment CT scans of all subjects were analyzed using Pulmo-CMS software (Medis Specials, Leiden, The Netherlands). Quantitative densitometry was performed

by calculating the Relative Area (RA) of pixel values below -950 Hounsfield Units in 12 axial partitions of equal volume in each lung [20]. The top and bottom partitions were excluded to prevent influence by partial volume effects, and each lung was then characterized by its RA slope, defined as the slope in the plot of RAs against partitions.

The ADO score (age, dyspnoea, obstruction) was calculated to allow us to quantify expected three year mortality in the patients at baseline [21].

Statistical analysis

Baseline parameters in patients with and without atelectasis were compared using appropriate test for paired comparisons. Primary analysis was survival at 6 years follow up in individuals with or without atelectasis. A secondary analysis compared survival in exercise 'improvers.' Other treatment response characteristics of survivors were compared to those who had not survived. All 'treatment response' parameters were measured one month post procedure.

RESULTS

Baseline characteristics of patients with (n=5) or without (n=14) atelectasis are given in Table 1. At 6 years, all five of the atelectasis group were still alive whereas 8 (57%) of the 14 non-atelectasis group had died (Chi^2 p=0.026) (Figure 1). Death certificate data showed that 6 deaths were from respiratory failure, one was cardiovascular and one was due to lung cancer. In a stepwise regression model atelectasis was retained as an independent correlate of survival at 6 years (R 0.51 p=0.026) whereas FEV_1 %

predicted, age and BMI were not. If the two non-respiratory deaths are excluded there is still a significant association between the occurrence of atelectasis and survival at 6 years (Chi^2 3.9 p=0.049)

With the exception of BMI, which was significantly higher in the atelectasis group; 28.4(2.9) vs 21.6(2.9) kgm^{-2} ($p<0.001$), there were no significant differences between the two groups at baseline in spirometry, lung volumes, gas transfer, blood gas parameters, quality of life, number of exacerbations in the preceding year or exercise capacity (assessed both by incremental shuttle walking test and cycle ergometry). In patients who did not have atelectasis there was no difference in BMI between those who were or were not alive at 6 years; 21.5(12.5) kgm^{-2} vs 21.7(6.6) kgm^{-2} (p=0.9).

Pre treatment CT appearances did not differ significantly between the atelectasis and non-atelectasis groups in terms of degree of emphysema at either the upper or lower parts of the lungs or in heterogeneity (slope) in either the treated or non-treated lung prior to treatment. Using the ADO score, predicted 3 year mortality was 31.1(10.0)% in the non-atelectasis group and 32.2(15.1)% in the atelectasis group (p=0.8). 4 of the 8 deaths occurred within 3 years of the procedure, representing a 16% three year mortality rate for the whole study group and a 29% mortality rate for the non-atelectasis group.

Acute effects of BLVR

As reported previously, BLVR was associated with an increase in cycle endurance time from 227(129) secs to 315(195) seconds (p=0.03), a fall in functional residual capacity from 7.1(1.5) to 6.6(1.7)L (p=0.03), and an increase diffusing capacity from

3.3(1.1) to 3.7(1.2) mmol.minute^{-1}.kPa^{-1} (p=0.03). Nine patients were defined as improvers in the original study on the basis of their exercise capacity. At 6 years, 2(22%) of the improvers and 6 (60%) of the non-improvers had died (p=0.06) (Figure 2).

Comparison of early responses between patients who had died or were still alive at six years are given in table 2. Of note, although survivors had numerically better responses for all parameters, only the occurrence of atelectasis was significantly different between groups.

Late complications

In the atelectasis group, as previously reported, one pneumothorax requiring intercostal drainage occurred at day two and one, which resolved without intervention, occurred at 4 weeks. There were no pneumothoraces in the non-atelectasis group. Subsequently one patient who had atelectasis developed a distal lung infection requiring drainage 6 years post procedure and one patient without atelectasis developed an ipsilateral empyema 2 years post procedure.

Follow up imaging was not performed systematically, but CT or chest x-ray appearances were consistent with persisting atelectasis in all patients for at least one year (mean follow up at time of imaging 5.5 years) where this had been present at the one month scan.

DISCUSSION

The main finding of this study is that the occurrence of atelectasis following BLVR for severe emphysema is associated with prolonged survival, with 100% alive at 6 years compared to only 43% of individuals where atelectasis had not occurred. The only parameter that differed at baseline was BMI, which was significantly higher in the atelectasis group, but BMI was not itself independently associated with survival.

Significance of findings

The first possibility is that the survival advantage is explained by a difference in the baseline characteristics of the participants i.e. that some factor predisposing individuals to develop atelectasis also improved outcomes. A number of factors have been associated with survival in COPD including lung function parameters, exercise capacity, breathlessness and exacerbation frequency [22]. The participants in this study were thoroughly phenotyped (Table 1) and did not differ significantly at baseline in any parameter except in their BMI, which was higher in the atelectasis group. Exacerbation rate and quality of life were numerically but not significantly worse in the atelectasis group at baseline. A low BMI (<21) is an element of the BODE index which predicts survival in COPD although it wields only a modest effect and did not differ between survivors and non-survivors in the atelectasis group [23]. The lack of difference in BMI between survivors and non-survivors in the non-atelectasis group suggests that it was not a significant factor determining survival and it is unlikely to be the explanation for the marked difference in outcome we observed. Moreover, in a study from our group based on a similar hospital-based COPD cohort, following 110 patients with a mean FEV_1 of 36.6% predicted for up to five years, BMI did not differ between those who had died (n=37) and survivors (n=73); 25(6.4) kgm^{-2} vs 25.1(6.4) kgm^{-2} [24].

Another possibility is that the presence of atelectasis led to a systematic difference in the way that patients were treated subsequently that influenced survival. Patients were on standard optimal inhaled therapy already and it is likely that if a change occurred at all it would have led to a reduction in therapy in the atelectasis group so it is not clear how this would have conferred a survival advantage.

There are a number of factors by which atelectasis might provide a survival advantage in patients with severe emphysema. Lung volume reduction surgery is associated with improved survival and exercise capacity in subgroups with low exercise capacity and heterogeneous disease [2], and is also associated with an improvement in diaphragm strength [25] and a reduction in the oxygen cost of breathing [26]. Successful BLVR, where atelectasis occurred, is likely to have mimicked the effects of LVRS by reducing operating lung volumes. Measures of gas trapping IC/TLC ratio[27] and sniff nasal pressure [24] have been shown to be associated with mortality in COPD, and both lung volumes and diaphragm function improved most in the atelectasis patients [14]. In this study cohort dynamic hyperinflation also improved most in patients with atelectasis. Dynamic hyperinflation has been shown to be associated with reductions in daily physical activity [28] which is itself associated with accelerated disease progression [29] and increased co-morbidity [30]. Interestingly a reduction in systemic inflammation has been observed following LVRS [31] – the authors of that study suggest that this is because of the removal of diseased lung but an alternative hypothesis is that a reduced work of breathing leads to a reduction in sympathetic activation [32] and reduced cardiac compromise from hyperinflation

[33]. This would be an interesting hypothesis to test in subsequent studies with BLVR approaches.

None of the deaths in our cohort occurred within 6 months of the procedure, making it unlikely that they were related directly to complications of the procedure itself, which continues to have a better safety profile than LVRS [2, 9, 16].

The current data suggest a survival benefit associated with improvement in functional capacity as there were fewer deaths in the 'improvers' group, defined as those with a >60 second improvement in endurance cycle time, though this is less clear cut than the effect of atelectasis. Interestingly although survivors tended to have had a better lung function and exercise response to BLVR at one month (Table 2) the only response parameter that was significantly different between the two groups was the occurrence of atelectasis.

Implications for targeting strategy

In a multicentre series of 98 patients treated with Emphasys valves, 5 pneumothoraces occurred, 3 requiring surgical intervention [9]. All pneumothoraces occurred where lobar occlusion had been performed. In that study, a lobar targeting strategy produced significantly better improvements in FEV_1 and exercise capacity than a nonlobar approach. Likewise, a unilateral approach led to greater benefits in FEV_1 and exercise capacity than a bilateral approach. No data on radiological atelectasis were presented however. There were no obstructive pneumonias and in fact 5 pneumonias occurred in non-targeted lobes during the 90 day follow up period.

The VENT study (Endobronchial Valve for Emphysema Palliation Trial) was a randomized controlled trial studying the addition of BLVR to best supportive care including pulmonary rehabilitation. A unilateral lobar targeting strategy was adopted. The study results have not yet been published fully, but the BLVR intervention was associated with an improvement in FEV_1 and exercise capacity [4]. Functional improvement and reduction in lobar volume were greatest in those with intact interlobar fissures, the absence of defects being a marker for reduced collateral ventilation [34].

In contrast to the unilateral lobar occlusion strategy, a bilateral approach with incomplete lobar occlusion has also been advocated in trials with the umbrella-shaped IBV valve (Spiration Inc, Redmond, Wash, USA). A review of experience in 98 subjects undergoing bilateral valve placement found that although treatment was associated with changes in lobar volume and improvements in quality of life (which must be interpreted with great caution in the absence of a control group), there were no changes in lung function parameters. Interestingly this group also found that where atelectasis, which occurred in 9(9%) subjects, was present it was associated with significant improvements in lung volumes as well as larger improvements in SGRQ[16]. Pneumothorax occurred in 5 (56%) atelectasis patients and 6 (7%) of the non-atelectasis patients. Longer term follow up data from that cohort is not available.

Limitations of the study

The study is relatively small and confirmation from larger cohorts and trials is necessary. An incremental shuttle walk test was used rather than the 6 minute walk

test, so it was not possible to calculate the BODE score for these patients. However the ADO index suggests an expected 3 year mortality of more than 30 percent in the whole cohort, similar to the 29% 3 year mortality observed in the non-atelectasis group. This suggests that the finding of prolonged survival in the atelectasis group differs significantly from what would have been expected.

Conclusion

These data suggest that where BLVR is successful in producing atelectasis this imparts a significant survival advantage. The data also illustrate that longer term follow up is needed to evaluate fully the risks and benefits of bronchoscopic lung volume procedures.

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NSH conceived the study, analyzed the data and wrote the first draft of the manuscript. SVK and DMH performed the radiological analysis. DMG, DMH, MIP, TPT, NSH were involved in the original procedures, results of which are followed up in this study. All authors contributed to and approved the final paper.

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Figure 1

Atelectasis following BLVR was associated with improved survival (p=0.026).

Figure 2

There were fewer deaths among patients with a significant improvement in exercise capacity after BLVR (p=0.06).

Table 1: Baseline characteristics

	Non-atelectasis =14	atelectasis n=5	T test
Age	59.6(9.0)	56.0(7.6)	0.4
Percent female	14	20	0.7
BMI ($kg.m^{-2}$)	21.6(2.9)	28.2(2.9)	0.004
SNiP (cmH_2O)	64.4(22.9)	70.6(26.3)	0.6
FFMI ($kg.m^{-2}$)	15.8(1.5)	17.5(1.4)	0.05
SGRQ Symptoms	63.3(18.2)	64.9(24.3)	0.9
SGRQ Activity	76.9(18.1)	83.2(11.0)	0.5
SGRQ Impacts	42.8(13.9)	51.9(11.0)	0.2
SGRQ Total	56.5(14.2)	63.5(5.3)	0.3
SF-36 PCS	41.2(19.9)	41.9(16.9)	0.9
SF-36 MCS	50.5(23.4)	50.7(19.3)	0.9
FEV_1 %pred	28.6(11.8)	27.7(13.3)	0.9
FVC %pred	80.1(18.2)	81.0(34.3)	0.9
TLC %pred	141.1(16.0)	134.3(14.7)	0.4
RV %pred	264.4(66.6)	249.4(80.0)	0.7
RV/TLC (%)	64.0(10.8)	60.9(16.1)	0.6
FRC %pred	213.3(37.9)	200.1(44.1)	0.5
TLco %pred	35.6(11.2)	36.9(11.1)	0.8
$PaCO_2$ (kPa)	4.8(0.5)	4.8(0.8)	0.9
PaO_2 (kPa)	10.0(1.4)	9.2(1.7)	0.3
Exacerbation rate /yr	1.9(1.5)	2.8(2.7)	0.4
ADD prednisone mg/day	3.1(6.3)	4.1(5.6)	0.8
Pack years smoked	45.4(16.7)	58.6(21.9)	0.2
VO_2 l/min	0.85(0.23)	0.85(0.26)	0.99
VCO_2 l/min	0.79(0.27)	0.79(0.23)	0.98
VE l/min	29.5(9.9)	29.5(4.1)	0.99

Values are Mean (SD). BMI body mass index, SNiP sniff nasal inspiratory pressure, FFMI fat free mass index, SGRQ St George's Respiratory Questionnaire, SF-36 short form 36, PCS physical component score, MCS mental component score, FEV_1 forced expiratory volume in one second, TL_{CO} diffusing capacity, TLC total lung capacity, RV residual volume, FRC functional residual capacity. ADD average daily dose in the preceding year, VO_2 oxygen consumption, VCO_2 carbon dioxide production, VE minute ventilation.

Table 2 Comparison of early responses to BLVR in survivors and non-survivors

	Non-survivor at 6 years =8	Survivor at 6 years n=11	p
Δ SWT (m)	+17.5 (65)	20.9(95)	0.9
Δ TLco (mmol.minute^{-1}.kPa^{-1})	+0.11(0.4)	+0.46(0.6)	0.2
Δ RV (L)	-0.01(0.4)	-0.62(1.2)	0.37
Δ TLC (L)	-0.17(0.28)	-0.31(0.55)	0.53
Δ FRC (L)	-0.26(0.41)	-0.49(0.86)	0.53
Δ Endurance time (secs)	+26.5(148)	+133 (172)	0.17
Δ FEV_1 (L)	-0.01(0.17)	+0.18(0.2)	0.06
Δ Isotime EELV (L)	-0.16(0.56)	-0.61(1.0)	0.31
Δ SGRQ	-0.6(10.6)	-0.1(8.4)	0.9
Atelectasis (n)	0	5(45%)	0.026*

Values are Mean (SD). SWT shuttle walk test, TL_{CO} diffusing capacity, RV residual volume, TLC total lung capacity, Endurance time refers to performance on a cycle ergometer at 80% of peak workload, FEV_1 forced expiratory volume in one second, EELV end expiratory lung volume, SGRQ St George's respiratory questionnaire total score. P values are for unpaired t tests except *Chi^2.