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# Atelectasis and survival after bronchoscopic lung volume reduction for COPD

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**ABSTRACT: Bronchoscopic therapies to reduce lung volumes in chronic obstructive pulmonary disease are intended to avoid the risks associated with lung volume reduction surgery (LVRS) or to be used in patient groups in whom LVRS is not appropriate. Bronchoscopic lung volume reduction (BLVR) using endobronchial valves to target unilateral lobar occlusion can improve lung function and exercise capacity in patients with emphysema. The benefit is most pronounced in, though not confined to, patients where lobar atelectasis has occurred. Few data exist on their long-term outcome.**

**19 patients (16 males; mean±SD forced expiratory volume in 1 s 28.4±11.9% predicted) underwent BLVR between July 2002 and February 2004. Radiological atelectasis was observed in five patients. Survival data was available for all patients up to February 2010.**

**None of the patients in whom atelectasis occurred died during follow-up, whereas eight out of 14 in the nonatelectasis group died (Chi-squared $p=0.026$). 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 computed tomography appearances, although body mass index was significantly higher in the atelectasis group (21.6±2.9 *versus* 28.4±2.9 $kg \cdot m^{-2}$; $p<0.001$).**

**The data in the present study suggest that atelectasis following BLVR is associated with a survival benefit that is not explained by baseline differences.**

**KEYWORDS: Emphysema, interventional bronchoscopy, mortality**

Despite optimal pharmacological therapy and pulmonary rehabilitation, patients with chronic obstructive pulmonary disease (COPD) remain significantly disabled. Lung volume reduction surgery (LVRS) has been clearly shown to improve outcomes in selected patient groups [1–3]. This surgical intervention is, however, associated with significant morbidity and an early mortality rate of ~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 the worst affected areas; the PneumRx™ coil (PneumRx Inc., Mountain View, CA, USA) 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, we published a case series describing the effect of bronchoscopic lung volume reduction (BLVR), using the Emphasys™ valves (Emphasys Medical Inc., Redwood City, CA, USA) in patients with severe emphysema [14]. The procedure was associated with improvements in exercise capacity that were most pronounced in, but not confined to, individuals with radiological atelectasis. 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

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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 as 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 our original study was reviewed and related to treatment response and baseline characteristics.

## METHODS

Between July 2002 and February 2004, 19 patients (16 males; mean±SD forced expiratory volume in 1 s ($FEV_1$) 28.4±11.9% predicted) underwent BLVR at The Royal Brompton Hospital, London, UK. Vital status was established for all the participants up to February 2010 (*i.e.* 6 yrs after the final procedure was completed) and survival data was censored at 6 yrs. 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 4-week outcomes has been published previously [14]. To recap briefly, patients were eligible to participate if they had COPD consistent with the Global Initiative for Obstructive Lung Disease (GOLD) guidelines [18], significant dyspnoea despite optimum medical therapy (including pulmonary rehabilitation), and a heterogeneous pattern of disease with a target area identified by computed tomography (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.) placed to occlude segmental bronchi leading to the most affected area of the 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, 1–2 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 1 month post-procedure.

Spirometry, gas transfer and lung volumes assessed by body plethysmography were measured using a CompactLab System (Jaeger, Hoechberg, Germany). Arterial oxygen and carbon dioxide tension were measured in arterialised earlobe capillary samples. Quality of life was assessed using the St George's Respiratory Questionnaire (SGRQ) and the Short Form-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 $\geqslant$60 s and a 30% increase in endurance time.

Pre-treatment CT scans of all subjects were analysed using Pulmo-CMS software (Medis Specials, Leiden, the Netherlands). Quantitative densitometry was performed by calculating the relative area (RA) of pixel values < -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 characterised 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 3-yr mortality in the patients at baseline [21].

### *Statistical analysis*

Baseline parameters in patients with and without atelectasis were compared using appropriate tests for paired comparisons. The primary analysis was survival at 6-yr 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 1 month post-procedure.

## RESULTS

The baseline characteristics of patients with (n=5) or without (n=14) atelectasis are presented in table 1. At 6 yrs, all five subjects of the atelectasis group were still alive, whereas eight (57%) out of the 14 nonatelectasis subjects had died (Chi-squared p=0.026) (fig. 1). Death certificate data showed that six 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 yrs (r=0.51; p=0.026), whereas $FEV_1$ % pred, age and body mass index (BMI) were not. If the two nonrespiratory deaths are excluded, there is still a significant association between the occurrence of atelectasis and survival at 6 yrs (Chi-squared 3.9, respectively; p=0.049)

With the exception of BMI, which was significantly higher in the atelectasis group (28.4±2.9 *versus* 21.6±2.9 $kg \cdot m^{-2}$; 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 yrs (21.5±12.5 *versus* 21.7±6.6 $kg \cdot m^{-2}$; p=0.9).

Pre-treatment CT appearances did not differ significantly between the atelectasis and nonatelectasis 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 nontreated lung prior to treatment. Using the ADO score, predicted 3-yr mortality was 31.1±10.0% in the nonatelectasis group and 32.2±15.1% in the atelectasis group (p=0.8). Four out of the eight deaths occurred within 3 yrs of the procedure, representing a 16% 3-yr mortality rate for the whole study group and a 29% mortality rate for the nonatelectasis group.

### *Acute effects of BLVR*

As reported previously, BLVR was associated with an increase in cycle endurance time from 227±129 to 315±195 s (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 in diffusing capacity from 3.3±1.1

**TABLE 1** Baseline characteristics

| | Nonatelectasis | Atelectasis | p-value |
|---|---|---|---|
| **Subjects n** | 14 | 5 | |
| **Age yrs** | 59.6±9.0 | 56.0±7.6 | 0.4 |
| **Females %** | 14 | 20 | 0.7 |
| **BMI kg·m$^{-2}$** | 21.6±2.9 | 28.2±2.9 | 0.004 |
| **SNIP cm$H_2O$** | 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 |
| Activity | 76.9±18.1 | 83.2±11.0 | 0.5 |
| Impacts | 42.8±13.9 | 51.9±11.0 | 0.2 |
| Total | 56.5±14.2 | 63.5±5.3 | 0.3 |
| **SF-36** | | | |
| PCS | 41.2±19.9 | 41.9±16.9 | 0.9 |
| 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 |
| **$D_{L,CO}$ % pred** | 35.6±11.2 | 36.9±11.1 | 0.8 |
| **$P_{a,CO_2}$ kPa** | 4.8±0.5 | 4.8±0.8 | 0.9 |
| **$P_{a,O_2}$ kPa** | 10.0±1.4 | 9.2±1.7 | 0.3 |
| **Exacerbations per yr** | 1.9±1.5 | 2.8±2.7 | 0.4 |
| **ADD prednisone mg·day$^{-1}$** | 3.1±6.3 | 4.1±5.6 | 0.8 |
| **Smoking exposure pack-yrs** | 45.4±16.7 | 58.6±21.9 | 0.2 |
| **$V'_{O_2}$ L·min$^{-1}$** | 0.85±0.23 | 0.85±0.26 | 0.99 |
| **$V'_{CO_2}$ L·min$^{-1}$** | 0.79±0.27 | 0.79±0.23 | 0.98 |
| **$V'_E$ L·min$^{-1}$** | 29.5±9.9 | 29.5±4.1 | 0.99 |

Data are presented as mean±SD, unless otherwise stated. p-values are for unpaired t-tests. BMI: body mass index; SNIP: sniff nasal inspiratory pressure; FFMI: fat-free mass index; SGRQ: St George's Respiratory Questionnaire; SF: Short Form; PCS: physical component score; MCS: mental component score; $FEV_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon dioxide; $P_{a,CO_2}$: arterial carbon dioxide tension; $P_{a,O_2}$: arterial oxygen tension; ADD: average daily dose in the preceding year; $V'_{O_2}$: oxygen consumption; $V'_{CO_2}$: carbon dioxide production; $V'_E$: minute ventilation.

to 3.7±1.2 mmol·min$^{-1}$·kPa$^{-1}$ (p=0.03). Nine patients were defined as improvers in the original study on the basis of their exercise capacity. At 6 yrs, two (22%) of the improvers and six (60%) of the nonimprovers had died (p=0.06) (fig. 2).

Comparison of early responses between patients who had died or were still alive at 6 yrs are presented in table 2. Notably, 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 1 and one, which resolved without intervention, occurred at 4 weeks. There were no pneumothoraces in the nonatelectasis group. Subsequently, one patient who had atelectasis developed a distal lung infection requiring drainage 6 yrs post-procedure and one patient without atelectasis developed an ipsilateral empyema 2 yrs post-procedure.

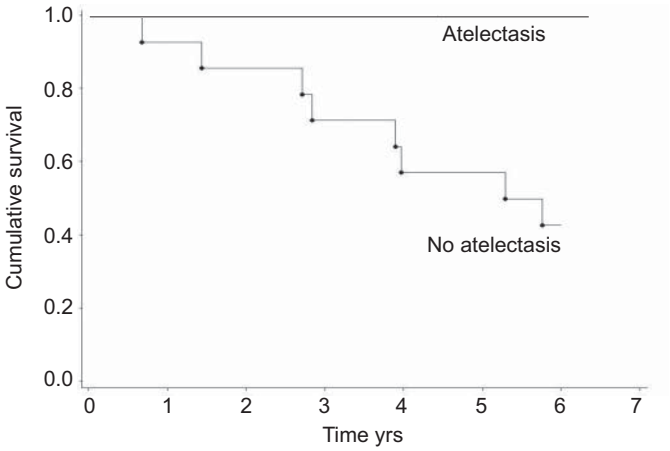


**FIGURE 1.** Atelectasis following bronchoscopic lung volume reduction was associated with improved survival (p=0.026).

Follow-up imaging was not performed systematically, but CT or chest radiographic appearances were consistent with persisting atelectasis in all patients for ⩾1 yr (mean follow-up at time of imaging 5.5 yrs) where this had been present at the 1-month scan.

## DISCUSSION

The main finding of this study was that the occurrence of atelectasis following BLVR for severe emphysema was associated with prolonged survival, with 100% alive at 6 yrs compared with 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.

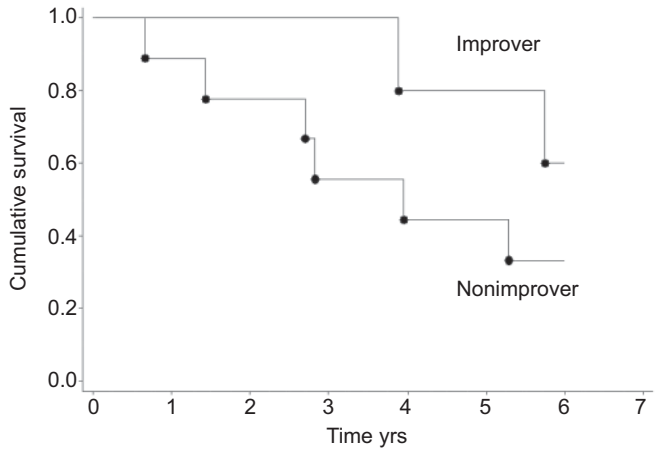


**FIGURE 2.** There were fewer deaths among patients with a significant improvement in exercise capacity after bronchoscopic lung volume reduction (p=0.06).

**TABLE 2** Comparison of early responses to bronchoscopic lung volume reduction in survivors and nonsurvivors

| | Nonsurvivor at 6 yrs | Survivor at 6 yrs | p-value |
|---|---|---|---|
| **Subjects n** | 8 | 11 | |
| **ΔSWT m** | 17.5±65 | 20.9±95 | 0.9 |
| **Δ$D_{L,CO}$ mmol·min$^{-1}$·kPa$^{-1}$** | 0.11±0.4 | 0.46±0.6 | 0.2 |
| **ΔRV L** | -0.01±0.4 | -0.62±1.2 | 0.37 |
| **ΔTLC L** | -0.17±0.28 | -0.31±0.55 | 0.53 |
| **ΔFRC L** | -0.26±0.41 | -0.49±0.86 | 0.53 |
| **Δendurance time s** | 26.5±148 | 133±172 | 0.17 |
| **Δ$FEV_1$ L** | -0.01±0.17 | 0.18±0.2 | 0.06 |
| **Δisotime EELV L** | -0.16±0.56 | -0.61±1.0 | 0.31 |
| **ΔSGRQ** | -0.6±10.6 | -0.1±8.4 | 0.9 |
| **Atelectasis** | 0 (0) | 5 (45) | 0.026# |

Data are presented as mean±SD or n (%), unless otherwise stated. Endurance time refers to performance on a cycle ergometer at 80% of peak workload. p-values are for unpaired t-tests. Δ: change in; SWT: shuttle walk test; $D_{L,CO}$: diffusing capacity of the lung for carbon dioxide; RV: residual volume; TLC: total lung capacity; FRC: functional residual capacity; $FEV_1$: forced expiratory volume in 1 s; EELV: end-expiratory lung volume; SGRQ: St George's Respiratory Questionnaire total score. #: Chi-squared test.

### *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 kg·m$^{-2}$) is an element of the BODE (BMI, degree of obstruction, dyspnoea, exercise capacity) index, which predicts survival in COPD, although it wields only a modest effect and did not differ between survivors and nonsurvivors in the atelectasis group [23]. The lack of difference in BMI between survivors and nonsurvivors in the nonatelectasis 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% pred for ⩽5 yrs, BMI did not differ between those who had died (n=37) and survivors (n=73) (25±6.4 *versus* 25.1±6.4 kg·m$^{-2}$, respectively) [24].

Another possibility is that the presence of atelectasis led to a systematic difference in the way that patients were treated subsequently, which influenced survival. Patients were on standard optimal inhaled therapy 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. LVRS 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 inspiratory capacity/total lung capacity 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]. 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 comorbidity [30]. Interestingly, a reduction in systemic inflammation following LVRS was observed by MINEO *et al.* [31]; the authors suggested 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-s 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 1 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, five pneumothoraces occurred, three of them 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, five pneumonias occurred in nontargeted lobes during the 90-day follow-up period.

The VENT study (Endobronchial Valve for Emphysema Palliation Trial) was a randomised controlled trial studying the addition of BLVR to best supportive care, including pulmonary rehabilitation. A unilateral lobar targeting strategy was adopted. The BLVR intervention was associated with small but statistically significant benefits in $FEV_1$ and exercise

capacity, compared with the control arm [4]. Functional improvement and reduction in lobar volume were greatest in those with intact interlobar fissures, with the absence of defects being a marker for reduced collateral ventilation.

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, WA, 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 was present, occurring in nine (9%) subjects, it was associated with significant improvements in lung volumes as well as larger improvements in SGRQ [16]. Pneumothorax occurred in five (56%) atelectasis patients and six (7%) of the nonatelectasis patients. Longer term follow-up data from that cohort is not available.

### *Limitations of the study*

The present study is relatively small and confirmation from larger cohorts and trials is necessary. An incremental shuttle walk test was used rather than the 6-min walk test, so it was not possible to calculate the BODE score for these patients. However, the ADO index suggests an expected 3-yr mortality of >30% in the whole cohort, similar to the 29% 3-yr mortality observed in the nonatelectasis 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.

## SUPPORT STATEMENT

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## STATEMENT OF INTEREST

Statements of interest for S.V. Kemp, P.L. Shah and M.I. Polkey can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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